A 58-year-old man with type 2 diabetes mellitus comes to the emergency department with fever, malaise, lower abdominal discomfort, and left flank pain. The patient has a history of diabetic autonomic neuropathy with bladder dysfunction and has been hospitalized multiple times for recurrent urinary tract infections. His temperature is 39.4 C (103 F), blood pressure is 94/50 mm Hg, and pulse is 118/min. Height is 180 cm (5 ft 11 in), weight is 150 kg (331 lb), and BMI is 46 kg/m^2. On examination, there is suprapubic and left costovertebral angle tenderness. After review of culture and sensitivity tests from his prior hospitalization, the patient is started on an empiric antibiotic regimen that includes an aminoglycoside. While calculating the appropriate dosage, the hospital pharmacy uses an adjusted body weight that is lower than the patient's actual body weight. Which of the following best explains the use of this adjusted parameter?

A. Distribution of the drug is limited to the extracellular fluid compartment

B. Elimination of the drug is predominately by hepatic clearance

C. Metabolism of the drug proceeds via zero-order kinetics

D. The drug exhibits a high degree of plasma protein binding

E. The drug is tightly sequestered within adipose tissues

Submit

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- ✓ A. Distribution of the drug is limited to the extracellular fluid compartment (36%)
- B. Elimination of the drug is predominately by hepatic clearance (8%)
- C. Metabolism of the drug proceeds via zero-order kinetics (8%)
- D. The drug exhibits a high degree of plasma protein binding (21%)
- E. The drug is tightly sequestered within adipose tissues (24%)

Omitted
Correct answer
A

36%
Answered correctly

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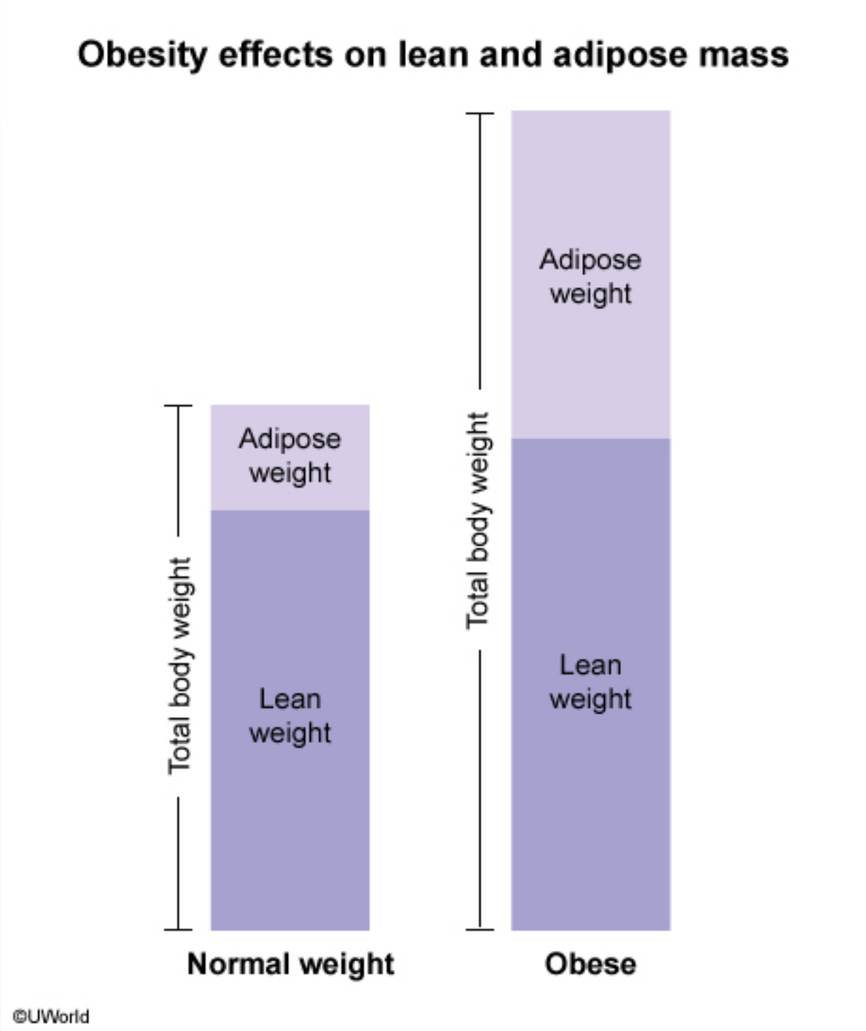
Time Spent

05/31/2020
Last Updated

Explanation

Obesity effects on lean and adipose mass



Drugs are typically dosed to maintain plasma drug concentrations within a target range. Although fixed drug dosing is convenient for providers and patients, dosing based on **body weight** (eg, mg/kg) is often used to improve safety and efficacy, particularly for medications with a narrow therapeutic window (eg, heparins, aminoglycosides, anesthetics).

Drugs are typically dosed to maintain plasma drug concentrations within a target range. Although fixed drug dosing is convenient for providers and patients, dosing based on **body weight** (eg, mg/kg) is often used to improve safety and efficacy, particularly for medications with a narrow therapeutic window (eg, heparins, aminoglycosides, anesthetics).

Body weight affects both the rate of drug clearance and the volume of distribution. Drug clearance rates correlate closely with lean body weight (ie, the weight of all nonadipose tissues, including muscle, liver, kidneys). Likewise, the volume of distribution for most drugs also gets larger as lean body mass increases. However, **obesity** causes a **disproportional increase in adipose mass**, which can have a variable effect on the volume of distribution depending on the solubility of the drug (eg, hydrophilic, hydrophobic).

Aminoglycosides are large, charged molecules that cannot cross cell membranes; their volume of distribution is limited to the extracellular space, which increases only marginally in obese individuals. As a result, **dosing in obese patients** is based on an **adjusted body weight** that takes into account only a portion (~40%) of the excess adipose mass.

(Choice B) The route of elimination does not directly impact weight-based drug dosing, aside from the fact that lipophilic drugs more often undergo hepatic elimination. Furthermore, aminoglycosides are not metabolized by the liver; they are freely filtered by the glomerulus and excreted unchanged in the urine.

(Choice C) The vast majority of drugs, including aminoglycosides, undergo first- (not zero-) order metabolism. In addition, body weight adjustments with regard to medication dosing are usually made according to the way a drug distributes within the body's tissues.

(Choice D) Acidic drugs with a high degree of plasma protein binding (eg, warfarin) are retained in the intravascular space and have a limited volume of distribution that is less affected by body weight. In contrast, aminoglycosides have minimal plasma protein binding and can distribute extensively into the interstitial compartment.

(Choice E) Lipophilic drugs partition extensively into adipose tissues; their volume of distribution is better correlated with total body weight than with lean or adjusted body weight. Highly lipophilic drugs (eg, phenytoin) are tightly sequestered within adipose tissue and often require an initial loading dose to saturate fat stores and achieve adequate serum levels.

Educational objective:
Many drugs are dosed based on total body weight to improve safety and efficacy. In obese individuals, use of lean body weight or an adjusted body weight may be necessary when dosing hydrophilic drugs (eg, aminoglycosides) that do not distribute into adipose tissue.

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References

- Drug dosing in obese adults.

Pharmacology	General Principles	Volume of distribution
Subject	System	Topic

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A 57-year-old Caucasian male with severe pyelonephritis is admitted to the hospital. His past medical history is significant for diabetes, hypertension, and two episodes of transient ischemic attacks. His serum creatinine level is 3.2 mg/dL; therefore, he needs to be started on an antibiotic that depends mainly on non-renal clearance. Which of the following characteristics should the antibiotic also have if hepatic metabolism and clearance is desired?

A. Low volume of distribution

B. Poor oral absorption

C. High lipophilicity

D. Low rate of redistribution

E. Poor penetration into the CNS

Submit

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- A. Low volume of distribution (17%)
- B. Poor oral absorption (8%)
- ✓ C. High lipophilicity (57%)
- D. Low rate of redistribution (12%)
- E. Poor penetration into the CNS (4%)

Omitted
Correct answer
C

57%
Answered correctly

02 secs
Time Spent

02/03/2020
Last Updated

Explanation

The kidney is the primary site of excretion of most drugs, with or without prior chemical modification in the liver. The liver is the major site of drug biotransformation and metabolism, but some drugs are also predominately eliminated by the liver into the bile and feces. Drugs with high intrinsic hepatic clearance tend to have high lipophilicity and a high volume of distribution. Highly lipophilic drugs tend to be poorly eliminated in the kidney as these agents rapidly cross tubular cell membranes after filtration to reenter the tissues.

High lipophilicity (lipid solubility) allows the drug to cross cellular barriers more easily and enter hepatocytes. It can then be excreted in the bile or

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High lipophilicity (lipid solubility) allows the drug to cross cellular barriers more easily and enter hepatocytes. It can then be excreted in the bile or through other methods of elimination. In addition, high lipid solubility assures a wide distribution to many different tissues including the brain, liver, and adipose tissue.

(Choice A) Drugs with a low distribution volume tend to be confined to the bloodstream and tend not to diffuse readily through hepatocytes into the bile. Thus, a drug with a low V_d will be highly plasma protein-bound and hydrophilic, making it less available for hepatic metabolism and more readily available for excretion unchanged in the urine.

(Choice B) A drug that is not well absorbed orally may have a high pre-systemic (first-pass) elimination or be poorly lipid-soluble. In both cases, it will be unavailable to the liver for hepatic clearance.

(Choice D) A low rate of redistribution from one compartment to another implies low lipid solubility or significant hydrophilicity. These drugs tend to remain in the intravascular compartment and be eliminated by the kidneys.

(Choice E) Poor central nervous system penetration indicates that a drug is likely not lipophilic, and therefore has a low volume of distribution. It is therefore also unlikely that the same drug will be eliminated in large amounts by the liver.

Educational Objective:
While the kidney is the primary site of elimination of most drugs, the liver is the main site of biotransformation of these agents in preparation for elimination. Drugs that are more lipophilic (high V_d, good penetration into CNS) are preferentially processed by the liver into more polar compounds for easier elimination in the bile and urine. Liver disease (e.g., cirrhosis) or the concomitant use of other drugs may limit or enhance the clearance of drugs metabolized in the liver.

Pharmacology	General Principles	Drug structure and properties

biotransformation and metabolism, but some drugs are also predominately eliminated by the liver into the bile and feces. Drugs with high intrinsic hepatic clearance tend to have high lipophilicity and a high volume of distribution. Highly lipophilic drugs tend to be poorly eliminated in the kidney as these agents rapidly cross tubular cell membranes after filtration to reenter the tissues.

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Pharmacology	General Principles	Drug structure and properties
Subject	System	Topic

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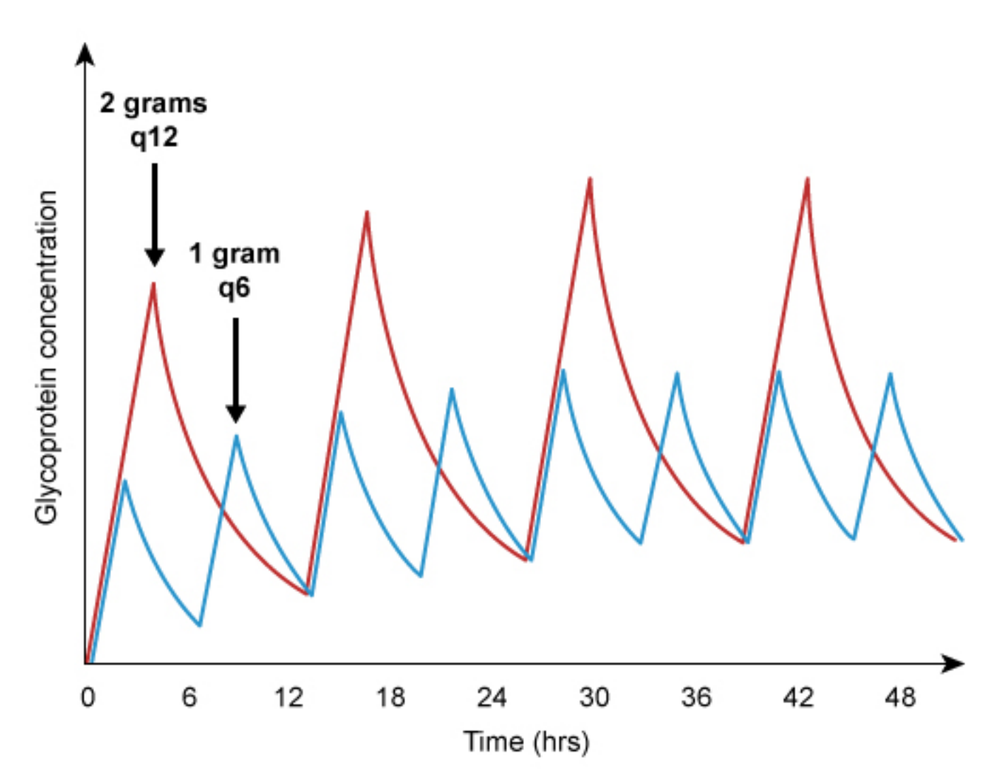
Researchers are developing a new glycopeptide antibiotic similar to vancomycin. Susceptibility testing reveals that the new drug is bactericidal against gram-positive organisms at serum concentrations above 15 µg/mL. Two different dosage regimens are developed to achieve a target serum trough concentration of 15-20 µg/mL: one administered as 1 gram every 6 hours and the other as 2 grams every 12 hours. The two regimens are tested in healthy volunteers during an early-phase clinical trial, and the following pharmacokinetic profiles are obtained.



Compared to the 12-hour dosing regimen, the 6-hour regimen is most likely to exhibit which of the following features?

A. Decreased renal clearance

B. Higher average plasma drug levels

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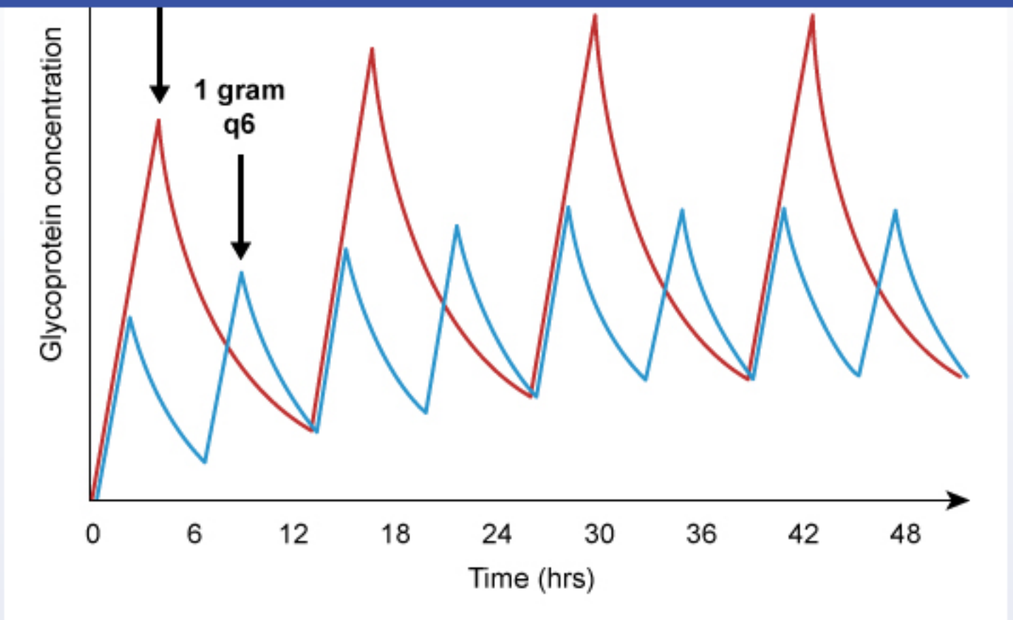

Compared to the 12-hour dosing regimen, the 6-hour regimen is most likely to exhibit which of the following features?

A. Decreased renal clearance

B. Higher average plasma drug levels

C. Improved patient compliance

D. Lower drug toxicity

E. Narrower therapeutic window

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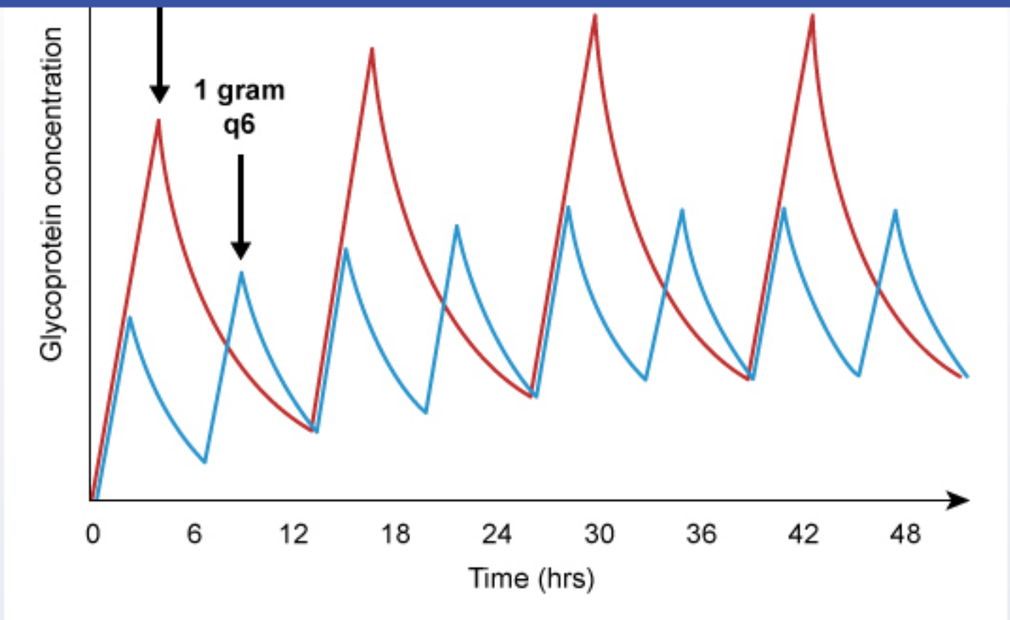

Compared to the 12-hour dosing regimen, the 6-hour regimen is most likely to exhibit which of the following features?

A. Decreased renal clearance (4%)

B. Higher average plasma drug levels (12%)

C. Improved patient compliance (2%)

✓ D. Lower drug toxicity (69%)

E. Narrower therapeutic window (10%)

Omitted
Correct answer

69%
Answered correctly

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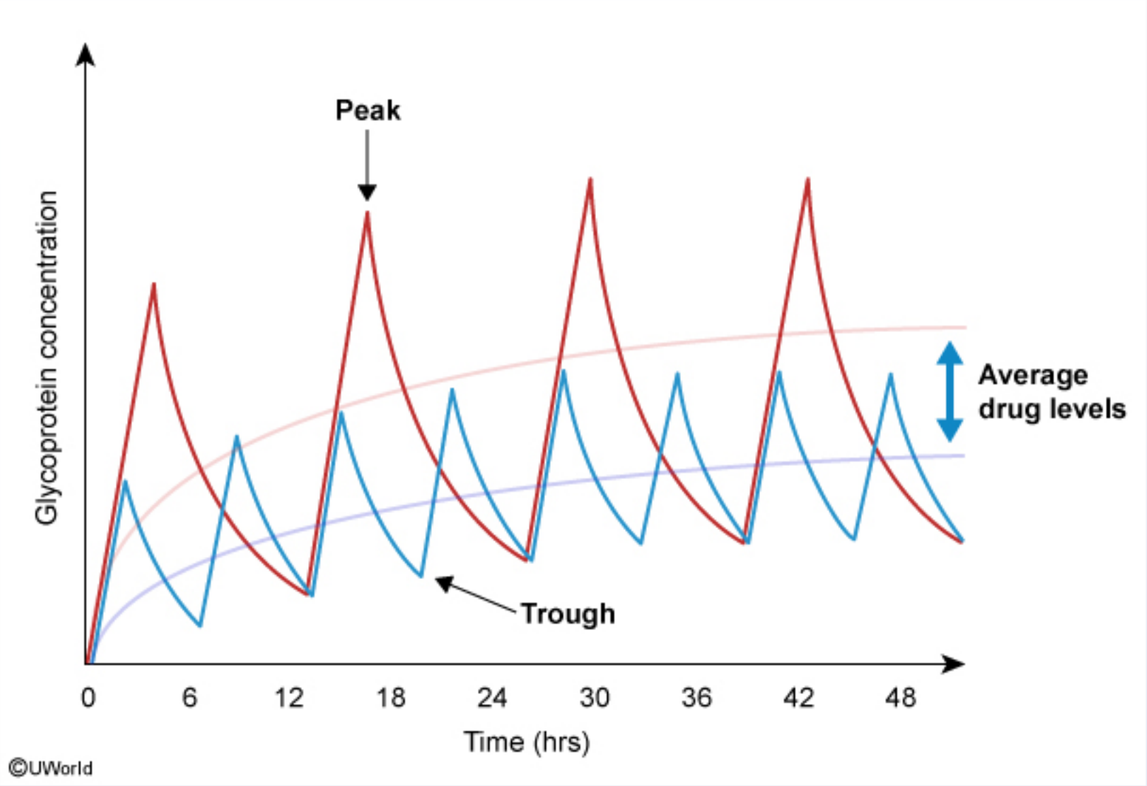

Drug dosing regimens are typically designed to maximize drug effectiveness and minimize toxicity. The above graph is comparing two different regimens with the same total dose (ie, 4 grams/24 hr) but with different dosing intervals (ie, 6 hr,12 hr). **Both regimens** have **similar trough levels** (ie, lowest concentration level before next dose) and maintain plasma levels above the bactericidal cutoff (eg, 15-20 µg/mL). As such, both regimens are likely to exhibit **similar efficacy**. However, **peak and average drug levels** are substantially **higher** with the **12-hour dosing regimen**. Because drug toxicity most often correlates with peak or average plasma drug levels, the **6-hour regimen** is likely to have **lower toxicity**.

(Choice A) Clearance (hepatic or renal) of a substance depends on the intrinsic properties of the agent. It is defined as the amount of plasma that is cleared of the drug over a given period (eg, mL/min). Drug clearance is typically the same regardless of the dosing schedule.

Time (hrs)

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(Choice B) Average plasma drug levels are lower when a fixed amount of drug is given in more divided doses. In this example, 4 grams are administered every 24 hours, either in 2 doses (12-hr regimen) or 4 doses (6-hr regimen). Therefore, the more frequent 6-hour regimen would result in lower average plasma drug levels.

(Choice C) Patient compliance is increased when the frequency of dosing is minimized. Only 2 doses per day are needed with the 12-hour regimen; however, the 6-hour regimen needs 4 doses and is likely to be more disruptive to the patient's schedule.

(Choice E) The therapeutic window refers to the range of drug dosages that have an appropriate clinical effect. It begins at the lowest dose at which the drug is effective and ends at the highest dose without significant toxic effects. Drugs with a narrow therapeutic window are often dosed more frequently to prevent large swings in plasma concentration.

Educational objective:
Drug dosing regimens with more frequent dosing have lower peak and average drug levels, which can help reduce drug toxicity.

Pharmacology	General Principles	Serum drug levels and half-life
Subject	System	Topic

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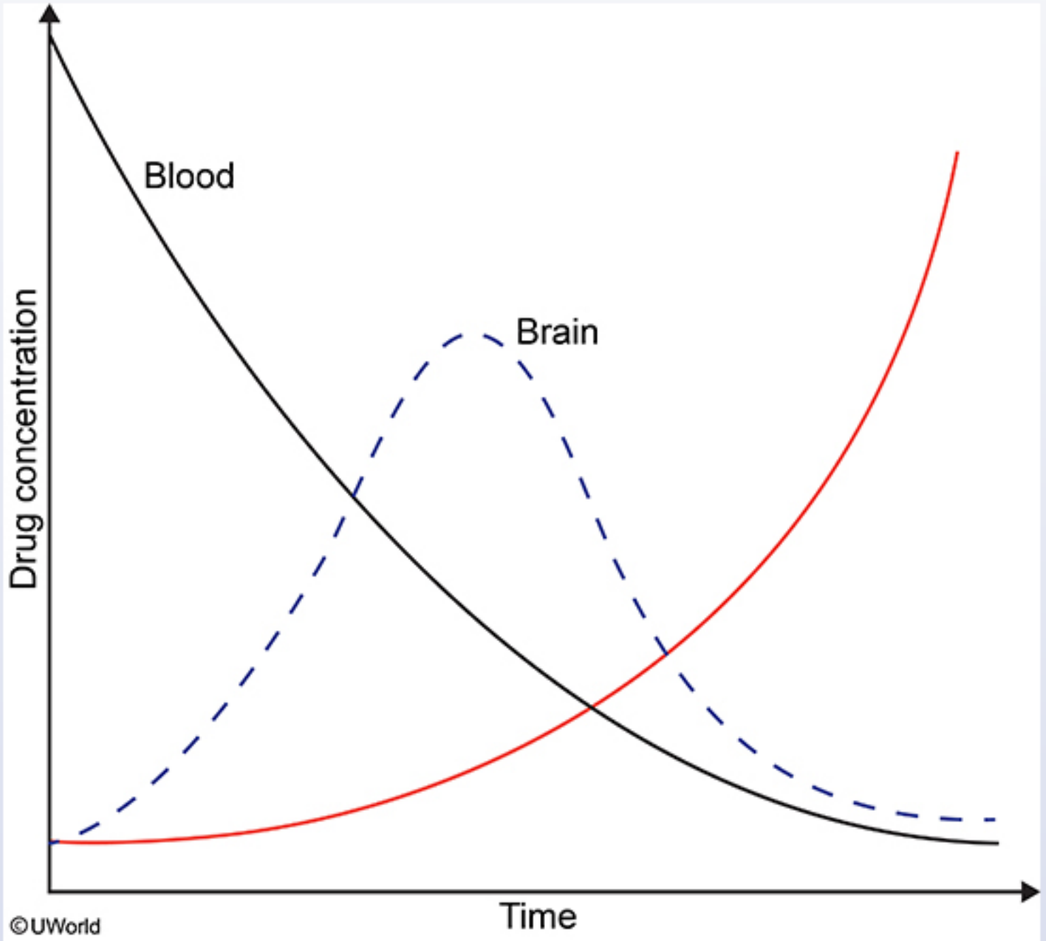
A group of investigators is studying the pharmacokinetic properties of the anesthetic drug propofol. A radiolabeled formulation of the drug is prepared and a single bolus is administered to adult guinea pigs. Blood and tissue samples are then collected at predetermined time intervals. Concentrations of the radioactive drug in the samples are assessed by liquid scintillation counting. The graph below demonstrates the drug concentration-time relationship in various tissues.



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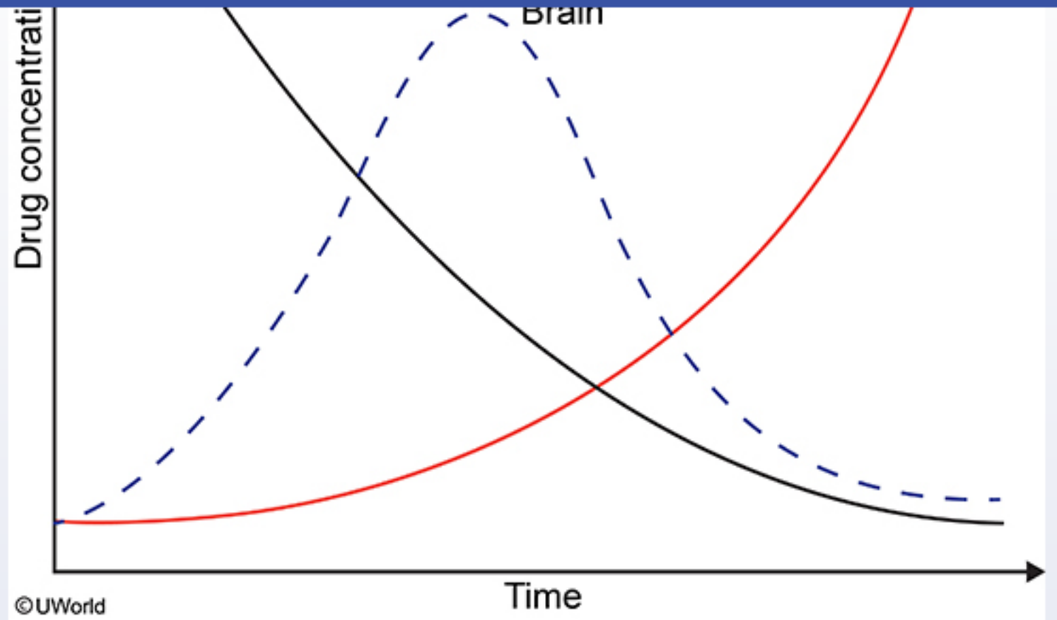

The red line on the graph most likely corresponds to which of the following tissues?

- A. Heart
- B. Kidney
- C. Liver
- D. Lungs
- E. Skeletal muscle

Submit

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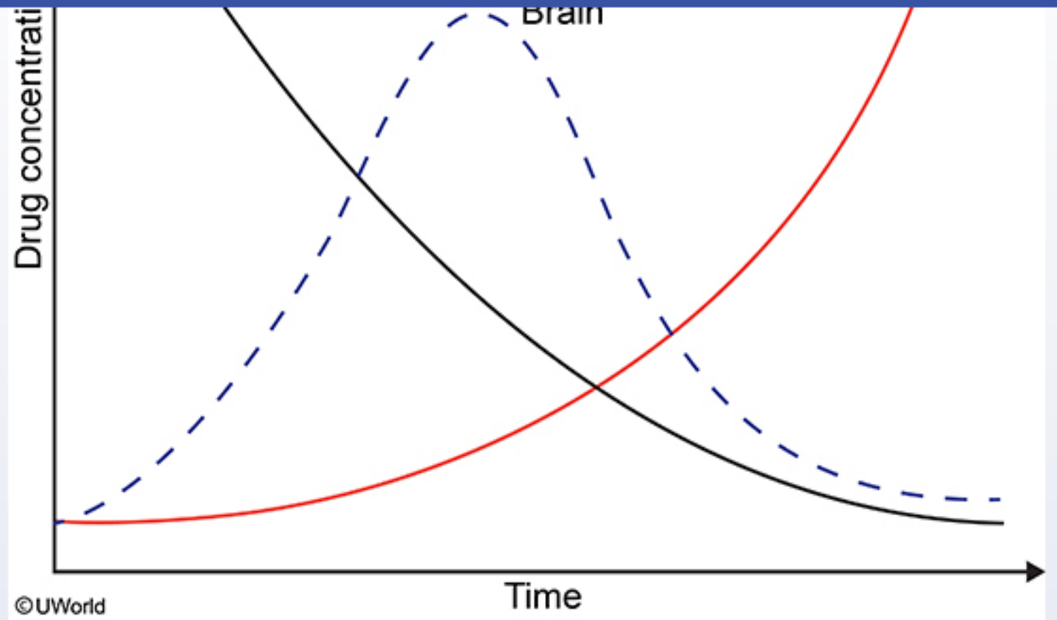

The red line on the graph most likely corresponds to which of the following tissues?

A. Heart (1%)
B. Kidney (18%)
C. Liver (29%)
D. Lungs (6%)
✓ E. Skeletal muscle (43%)

Omitted
Correct answer

43%
Answered correctly

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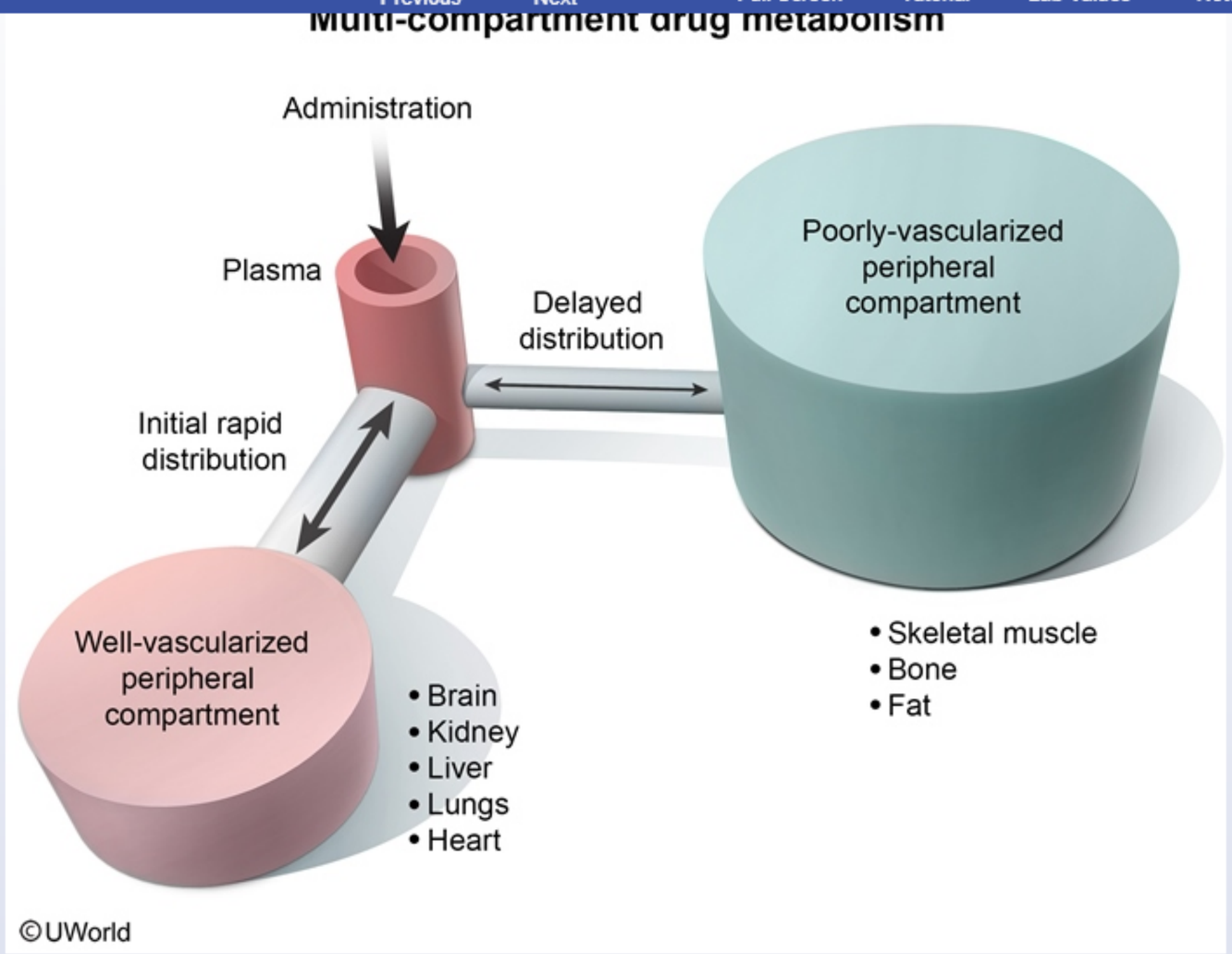

Drug distribution is not uniform; the rate at which drugs are delivered to target tissues is dependent on several factors, such as regional blood flow and drug characteristics. The pharmacokinetic profile of highly lipophilic anesthetic drugs, such as propofol, can be predicted using a **multi-compartment** model of distribution. Following administration of a single intravenous bolus, drug levels are high in the **central compartment** (ie, plasma). However, the drug is quickly distributed to the **well-perfused peripheral compartment** (eg, brain, liver, kidneys, lungs) due to the

- Brain
- Kidney
- Liver
- Lungs
- Heart
- Fat

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Over time, drug **redistribution** will occur through the central compartment into the **poorly-perfused peripheral compartment** (eg, skeletal muscle, fat, bone), which has the highest volume of distribution for lipophilic agents. Redistribution occurs rapidly with highly lipophilic drugs and is responsible for the short duration of action seen with commonly used anesthetics such as **propofol**.

(Choices A, B, C, and D) These organs have relatively high blood flow and are considered part of the well-perfused peripheral compartment. They will rapidly take up drugs from the central compartment and are visualized as the dashed line on the above graph.

Educational objective:
Following intravenous administration, a highly lipophilic drug will be rapidly distributed to organs with high blood flow (eg, brain, liver, kidneys, lungs). The drug is then redistributed to tissues with relatively lower blood flow (eg, skeletal muscle, fat, bone). This accounts for the short duration of action of many commonly used anesthetics, such as propofol.

Pharmacology	General Principles	Anesthesia
Subject	System	Topic

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An 82-year-old woman is brought to the office for a new patient evaluation. She recently moved in with her daughter. The patient reports frequent dizziness but cannot provide additional details regarding her symptoms. Medical history includes moderate dementia, hypertension, transient ischemic attack, depression, and chronic insomnia. Blood pressure is 124/72 mm Hg, and pulse is 66/min and regular. Neurologic examination shows disorientation to time and place but normal deep tendon reflexes and no focal sensory or motor deficits. The patient's medication schedule includes 12 different drugs that are used to manage her chronic conditions. Which of the following medications should be discontinued at this time?

A. Amlodipine
B. Aspirin
C. Diphenhydramine
D. Donepezil
E. Hydrochlorothiazide
F. Sertraline

Submit

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- A. Amlodipine (6%)
- B. Aspirin (0%)
- ✓ C. Diphenhydramine (81%)
- D. Donepezil (3%)
- E. Hydrochlorothiazide (3%)
- F. Sertraline (3%)

Omitted
Correct answer
C

81%
Answered correctly

02 secs
Time Spent

04/07/2020
Last Updated

Explanation

Common medications to avoid in older adults (Beers criteria)	
	• First-generation antihistamines

Common medications to avoid in older adults (Beers criteria)	
Anticholinergic	• First-generation antihistamines • Gastrointestinal antispasmodics
Cardiovascular	• Alpha-1 blockers (as antihypertensives) • Centrally acting alpha-2 agonists • Many antiarrhythmics
CNS	• Tricyclic antidepressants • Antipsychotics • Barbiturates, benzodiazepines & other hypnotics
Endocrine	• Long-acting sulfonylureas • Sliding-scale insulin
Pain	• Nonselective NSAIDs • Skeletal muscle relaxants

NSAIDs = nonsteroidal anti-inflammatory drugs.

Older patients are at increased risk for adverse effects of medications due to decreased drug clearance, cognitive and sensory deficits, multiple comorbidities, drug-drug interactions, and poor drug compliance. **Polypharmacy** (ie, ≥5 prescription and/or over-the-counter medications) is of particular concern in the elderly and can lead to a prescribing cascade, in which additional drugs are given for adverse effects that are misinterpreted as a new medical condition.

The **Beers criteria** were developed to identify drugs requiring caution in geriatric patients. **First-generation antihistamines** (eg, diphenhydramine) and other drugs with anticholinergic activity can increase the risk of confusion, hallucinations, dizziness, dry mouth, and constipation and should be avoided in this population. Other commonly used medications that should be avoided in the elderly include benzodiazepines (and other sedating medications), antipsychotics, many antiarrhythmics (eg, digoxin), and centrally acting skeletal muscle relaxants.

NSAIDs = nonsteroidal anti-inflammatory drugs.

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(Choices A and E) Although hypotension due to excessive antihypertension medication use could cause dizziness, this patient has normal blood pressure and heart rate, making this much less likely as a cause of her dizziness. In addition, although centrally acting alpha agonists (eg, clonidine) and alpha-1 blockers (eg, doxazosin) confer a high risk of orthostatic hypotension in elderly patients, thiazide diuretics (eg, hydrochlorothiazide), calcium channel blockers (eg, amlodipine), and ACE inhibitors/angiotensin II receptor blockers are generally considered acceptable for this population.

(Choice B) Aspirin should be used with caution in older adults due to the increased risk of gastric ulcer; however, the reduced risk of cardiovascular events provided by aspirin in patients with prior transient ischemic attack or stroke likely outweighs this risk.

(Choice D) Donepezil is a cholinesterase inhibitor that is commonly used in the treatment of Alzheimer dementia. Bradycardia can occasionally occur; however, this patient has a normal heart rate.

(Choice F) Selective serotonin reuptake inhibitors (eg, sertraline) are the preferred first-line medications for depression in older adults. Serotonin-norepinephrine reuptake inhibitors (eg, duloxetine) may also be used, especially for patients with chronic pain. Tricyclic antidepressants are relatively contraindicated in the elderly due to their anticholinergic effects.

Educational objective:
The Beers criteria identify drugs that should be used with caution in geriatric patients. Common drugs to avoid include anticholinergics (eg, first-generation antihistamines), centrally acting alpha-2 agonists, tricyclic antidepressants, benzodiazepines (and other sedating medications),

benzodiazepines (and other sedating medications), antipsychotics, many antiarrhythmics (eg, digoxin), and centrally acting skeletal muscle relaxants.

(Choices A and E) Although hypotension due to excessive antihypertension medication use could cause dizziness, this patient has normal blood pressure and heart rate, making this much less likely as a cause of her dizziness. In addition, although centrally acting alpha agonists (eg, clonidine) and alpha-1 blockers (eg, doxazosin) confer a high risk of orthostatic hypotension in elderly patients, thiazide diuretics (eg, hydrochlorothiazide), calcium channel blockers (eg, amlodipine), and ACE inhibitors/angiotensin II receptor blockers are generally considered acceptable for this population.

(Choice B) Aspirin should be used with caution in older adults due to the increased risk of gastric ulcer; however, the reduced risk of cardiovascular events provided by aspirin in patients with prior transient ischemic attack or stroke likely outweighs this risk.

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References

- American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults.

Pharmacology	General Principles	Polypharmacy
Subject	System	Topic

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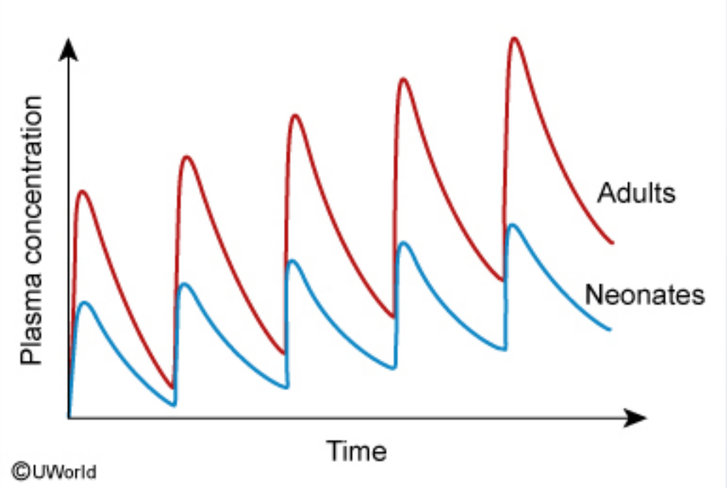
Researchers develop a novel glycopeptide antibiotic similar to vancomycin that is bactericidal against many gram-positive bacteria. From animal studies, they determine that the effective drug dosage is 5 mg/kg/day administered intravenously in divided doses. In a clinical trial, the antibiotic is administered to adult and neonatal patients with gram-positive infections. The drug is found to be effective in adults but not in neonates. During further analysis, plasma concentrations of the drug are measured in both groups, with the results shown in the image below:



Compared to adults, which of the following neonatal factors is the most likely cause of the difference in drug effectiveness?

- A. Decreased cytochrome P450 activity
- B. Decreased renal blood flow
- C. Elevated plasma protein level
- D. High body water content

Submit

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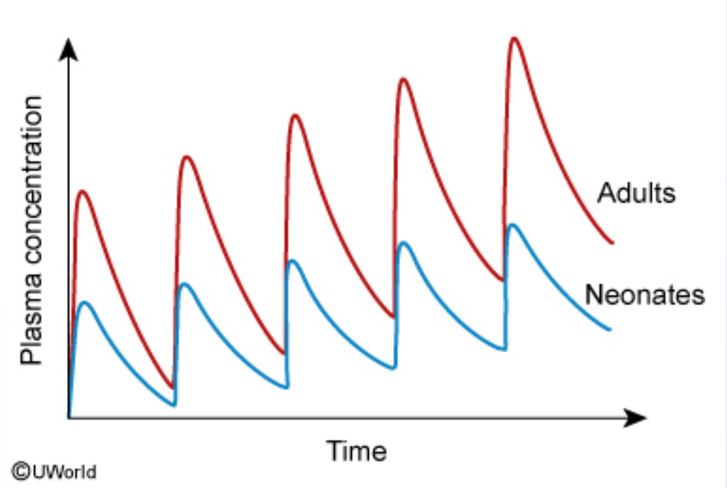

Compared to adults, which of the following neonatal factors is the most likely cause of the difference in drug effectiveness?

A. Decreased cytochrome P450 activity (25%)

B. Decreased renal blood flow (3%)

C. Elevated plasma protein level (26%)

✓ D. High body water content (43%)

Omitted 43% 02 secs 04/22/2020

Pharmacokinetic differences between neonatal patients and adults		
	Altered parameters	**Clinical effects**
Distribution	• ↑ Proportion of body water • Blood-brain barrier immaturity	• ↑ Distribution of water-soluble drugs may necessitate higher mg/kg dose • ↑ CNS toxicity
Metabolism	• ↓ CYP enzyme activity • ↓ Hepatic glucuronidation	• ↑ Sensitivity to hepatically metabolized drugs
Elimination	• ↓ Renal blood flow & GFR	• May require lower doses of renally excreted drugs

CYP = cytochrome P450; GFR = glomerular filtration rate.

In this example, a novel glycopeptide antibiotic is administered to adult and neonatal patients using the **same weight-based dosing regimen** (eg, 5 mg/kg). However, plasma concentrations of the drug are lower in **neonates** compared to the adults, resulting in **decreased effectiveness**.

Neonates have substantial pharmacokinetic differences compared to adult patients that affect drug absorption, distribution, and elimination. Changes in gastrointestinal parameters in neonates (eg, decreased gastric pH, reduced intestinal motility) can have a variable effect on the absorption of orally administered drugs. However, in this case, the drug is being administered **intravenously**, so changes in absorption are unlikely to be the cause of the plasma concentration discrepancy.

Neonates also have an **increased** proportion of **total body water** with a lower content of body fat compared to adults. This difference in body composition results in **water-soluble drugs** (eg, aminoglycosides, vancomycin) having a **larger than expected volume of distribution** relative to body mass, leading to **lower plasma concentrations** when the drug is administered at the same weight-based dosage as given to adult patients. Furthermore, neonates have an immature blood-brain barrier that increases the permeability of many substances into the CNS compartment, which (in addition to increasing the distribution volume) can increase the risk of CNS toxicity.

(Choice A) The liver is not fully developed in neonates and has decreased expression of drug-metabolizing enzymes (eg, cytochrome P450 isoenzymes, glucuronidation enzymes). This can lead to decreased clearance of drugs that are hepatically metabolized (eg, acetaminophen, morphine). However, this would result in increased (not decreased) plasma drug levels.

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(Choice B) Renal blood flow and glomerular filtration rate are decreased in neonates compared to adults. For drugs that are renally excreted, reduced renal clearance would cause increased serum drug concentrations, potentially leading to toxicity. However, in this study the serum concentration is lower in neonates than in adults.

(Choice C) Neonates have decreased (not increased) plasma protein concentrations compared to adults, which can increase free levels of highly protein-bound drugs (eg, phenytoin, penicillin). Elevated bilirubin levels in neonates can further increase the concentration of unbound drug by displacing them from albumin binding sites.

Educational objective:
Neonates have a higher proportion of body water compared to adults. This can result in lower plasma concentrations of water-soluble drugs if they are administered at the same weight-based dosage as given to adult patients.

Changes in gastrointestinal parameters in neonates (eg, decreased gastric pH, reduced intestinal motility) can have a variable effect on the absorption of orally administered drugs. However, in this case, the drug is being administered **intravenously**, so changes in absorption are unlikely to be the cause of the plasma concentration discrepancy.

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Educational objective:
Neonates have a higher proportion of body water compared to adults. This can result in lower plasma concentrations of water-soluble drugs if they are administered at the same weight-based dosage as given to adult patients.

Pharmacology	General Principles	Aging
Subject	System	Topic

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A group of investigators is currently conducting a phase I clinical trial for a newly developed synthetic opioid that has twice the analgesic capability of morphine. After oral ingestion of a fixed dose by several volunteers, the plasma concentration of the drug is measured and determined to be subtherapeutic. Rectal administration of the same dose of the drug shows a plasma concentration well within the therapeutic range, almost double the level measured after oral intake. Which of the following best accounts for the observed difference in drug concentration following rectal administration when compared to oral administration?

A. Decreased drug delivery to the liver

B. Greater blood flow to this region of the intestine

C. Increased absorption rate of the drug

D. Larger mucosal surface area

E. Reduced renal blood flow

Submit

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- ✓ A. Decreased drug delivery to the liver (70%)
- B. Greater blood flow to this region of the intestine (4%)
- C. Increased absorption rate of the drug (19%)
- D. Larger mucosal surface area (4%)
- E. Reduced renal blood flow (0%)

Omitted
Correct answer
A

70%
Answered correctly

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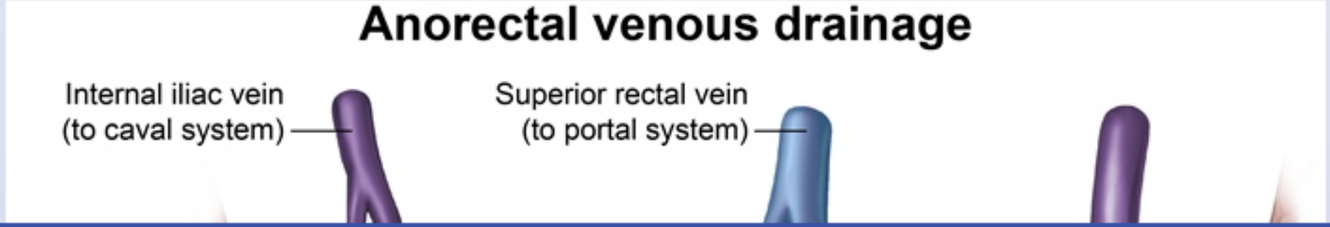
Time Spent

04/15/2020
Last Updated

Explanation



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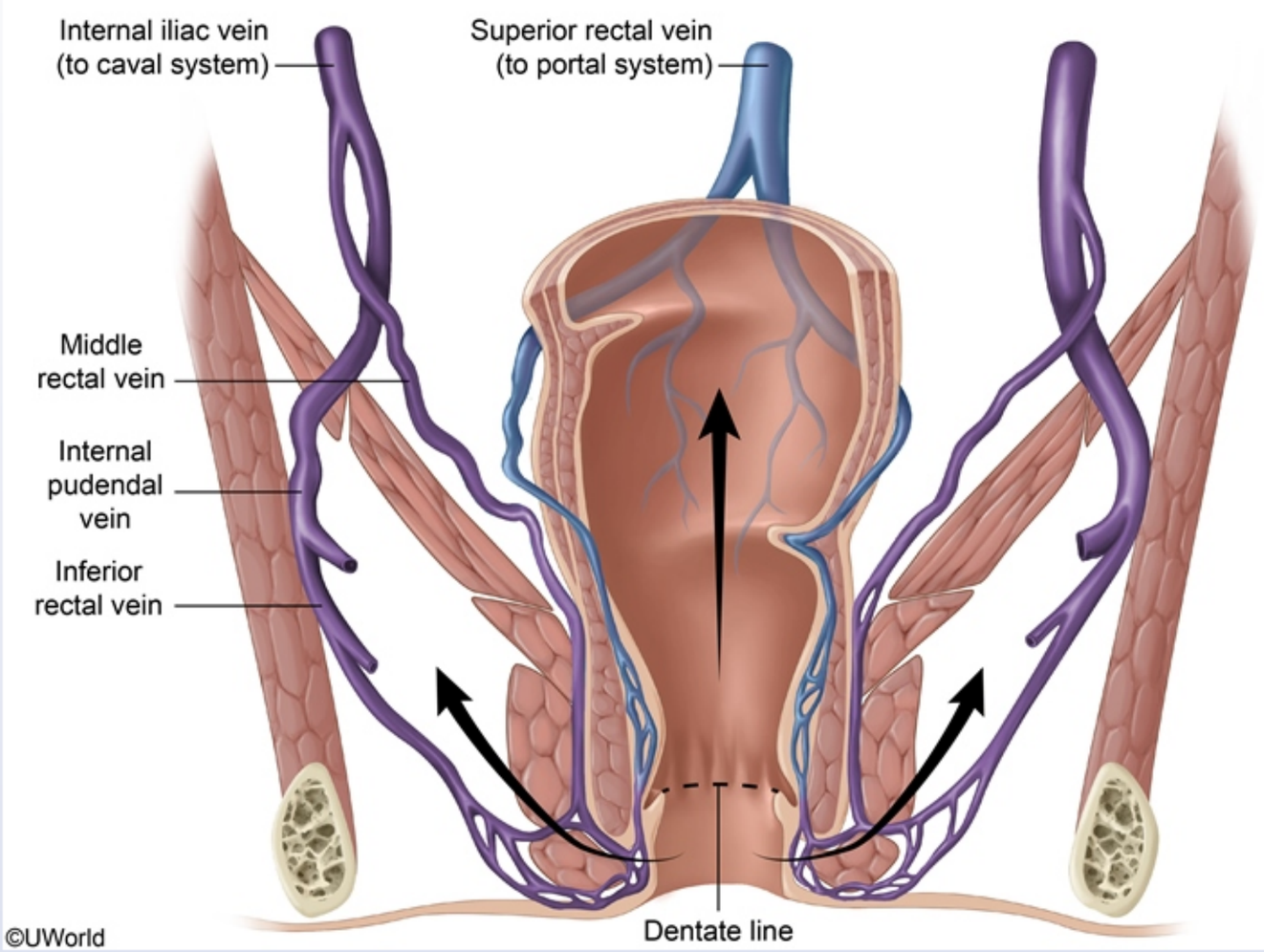
Anorectal venous drainage



Bioavailability is the fraction of an administered drug that reaches the systemic circulation unchanged. Oral bioavailability is dependent on the intrinsic absorptive properties of the drug as well as any **first-pass metabolism** that the drug undergoes by enzymes present in the intestine and liver. A drug that exhibits high first-pass metabolism is broken down extensively and will have a low concentration in the systemic circulation (low

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Rectal drug administration (suppository) allows for partial bypass of first-pass metabolism. Venous drainage of the anorectum above the dentate line is to the **portal venous system** via the superior rectal veins (drain to inferior mesenteric vein). However, the region below the dentate line drains into the systemic circulation via the middle and inferior rectal veins (drain to internal iliac and internal pudendal veins, respectively). This proportion of venous blood that enters the **systemic circulation** directly from the rectal region **increases the bioavailability** of drugs that are otherwise extensively metabolized by the liver following oral administration.

(Choice B) Blood flow to different regions of the intestine is directly related to the metabolic activity of the associated mucosa. Greater blood flow rates facilitate absorption and bioavailability of many drugs through the establishment of a favorable concentration gradient. The small intestine has greater blood flow than the colon due to the high rate of active transport required for nutrient digestion and absorption.

(Choices C and D) For drugs administered orally, the majority of absorption occurs in the small intestine due to its large surface area. In contrast, the surface area of the rectum is far smaller than that of the small intestine. Therefore, absorption of rectally administered drugs is typically slower and more unpredictable (due to variable amounts of stool) than that of orally administered drugs. This often necessitates more frequent or greater volume dosing to achieve similar blood concentrations in the absence of significant first-pass metabolism.

(Choice E) Changes in renal blood flow affect the glomerular filtration rate, which in turn affects the elimination of renally cleared drugs. Patients with impaired renal function have increased bioavailability of substances that are predominantly metabolized by the kidney; these patients may require lower doses to prevent adverse effects.

Educational objective:
Bioavailability is the fraction of an administered drug that reaches the systemic circulation unchanged. Drugs administered orally enter the portal circulation and are subject to first-pass metabolism. Rectal administration is capable of partially bypassing first-pass metabolism as a proportion of rectal blood flow enters the systemic circulation directly. Drugs that undergo extensive first-pass metabolism have increased bioavailability when administered rectally.

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References

- First-pass elimination. Basic concepts and clinical consequences.

Pharmacology	General Principles	Route of administration & bioavailability
Subject	System	Topic

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A 34-year-old woman comes to the physician for a follow-up visit. She was diagnosed with rheumatoid arthritis 3 months ago and started on methotrexate therapy. Despite treatment, she continues to have several hours of morning stiffness daily and frequently awakens at night due to joint pain. Physical examination shows swelling and tenderness in the joints of her hands and wrists. Etanercept is subsequently added to her treatment regimen. This medication is best characterized as which of the following?

A. Cell surface receptor antibody

B. Chimeric monoclonal antibody

C. Humanized monoclonal antibody

D. Small-molecule receptor inhibitor

E. Soluble receptor decoy protein

Submit

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- A. Cell surface receptor antibody (11%)
- B. Chimeric monoclonal antibody (9%)
- C. Humanized monoclonal antibody (10%)
- D. Small-molecule receptor inhibitor (13%)
- ✓ E. Soluble receptor decoy protein (54%)

Omitted
Correct answer
E

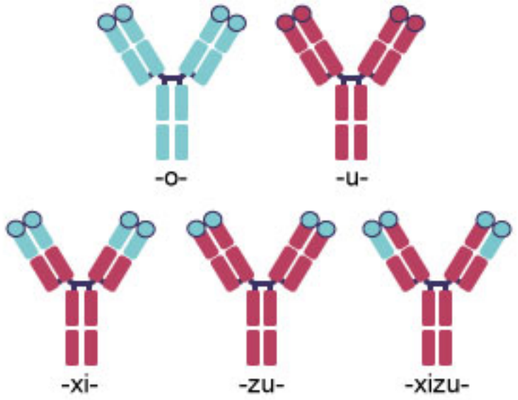
54%
Answered correctly

02 secs
Time Spent

04/14/2020
Last Updated

Explanation

Prefix	Target substem		Origin substem		Suffix
	Substem	Meaning	Substem	Meaning	
	*-b(a)**	Bacterial	-o-	Mouse	

Prefix	Target substem		Origin substem		Suffix
	Substem	**Meaning**	**Substem**	**Meaning**	
	*-b(a)**	Bacterial	*-o-*	Mouse	
	-c(i)-	Cardiovascular	*-u-*	Human	
	-f(u)-	Fungal	*-xi-*	Chimeric (human constant regions/ foreign variable regions)	
	-k(i)-	Interleukin	*-zu-*	Humanized (human constant & variable regions, except the complementarity determining regions)	
Variable	*-l(i)-*	Immunomodulating	*-xizu-*	Chimeric/humanized hybrid	-mab
	-n(e)-	Neural			-pab
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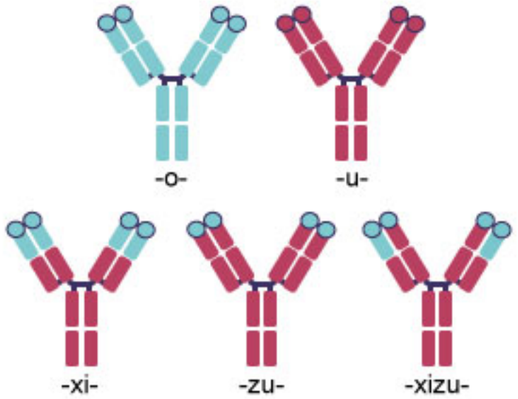
	-tox(a)-	Toxin			
	-t(u)-	Tumor			
	-v(i)-	Viral	Human parts are shown in red, nonhuman parts in blue. The complementarity determining regions		

Variable	*-l(i)-*	Immunomodulating	*-xizu-*	Chimeric/humanized hybrid	-mab
	-n(e)-	Neural	 Human parts are shown in red, nonhuman parts in blue. The complementarity determining regions are the circles on top of each antibody.		-pab
	-s(o)-	Bone			
	-tox(a)-	Toxin			
	-t(u)-	Tumor			
	-v(i)-	Viral			

* Vowel in parenthesis is used only when the origin substem begins with a consonant.

Mab = monoclonal antibody; **pab** = polyclonal antibody.

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Etanercept is a tumor necrosis factor-alpha (**TNF-α**) **inhibitor** added to methotrexate to treat moderate-to- severe rheumatoid arthritis in patients who have failed methotrexate alone. It is a **fusion protein** linking a soluble TNF-α receptor to the Fc component of human immunoglobulin G1 (IgG1). Etanercept reduces the biological activity of TNF-α by acting as a **decoy receptor**: the TNF-α receptor component acts like a sponge to bind TNF-α and keep it away from functional TNF-α receptors, while the Fc component stabilizes the complex.

Pharmaceutical companies provide the prefix of the names for biological agents; the suffix indicates whether the medication is a monoclonal antibody (*mab*), a receptor molecule (*cept*), or a kinase inhibitor (*nib*). Monoclonal antibodies, which are the largest group of biological agents, also include in their names the type of target (eg, bacterial or immune system) and their origin (eg, human or mouse).

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(Choice A) Rituximab (Ri-tu-xi-mab) is a chimeric monoclonal antibody targeted against CD20, a cell receptor found on the surface of B cells. It is used to treat CD20+ non-Hodgkin's lymphomas and other diseases related to excessive B-cell function.

(Choice B) Infliximab (Inf-li-xi-mab) is a chimeric monoclonal antibody targeted against TNF-α. It is used in the treatment of a number of autoimmune diseases (eg, rheumatoid arthritis and Crohn's disease).

(Choice C) Certolizumab pegol (Certo-li-zu-mab) is a pegylated (pegol) humanized monoclonal antibody that targets TNF-α. It lacks the Fc region, which helps minimizes complement activation and cell-mediated cytotoxicity that can occur with other anti-TNF-α medications that contain Fc domains.

(Choice D) Imatinib (Imati-nib) mesylate is used to treat specific cancers, including Philadelphia chromosome-positive chronic myelogenous leukemia and kit-positive gastrointestinal stromal tumors. It is an example of a small-molecule tyrosine kinase receptor inhibitor.

Educational objective:
The suffix of a biological agent indicates whether a medication is a monoclonal antibody (*mab*), a receptor molecule (*cept*), or a kinase inhibitor (*nib*). Monoclonal antibodies also include in their names the type of target (eg, bacterial or immune system) and their origin (eg, human or mouse).

Pharmacology	General Principles	Drug structure and properties
Subject	System	Topic

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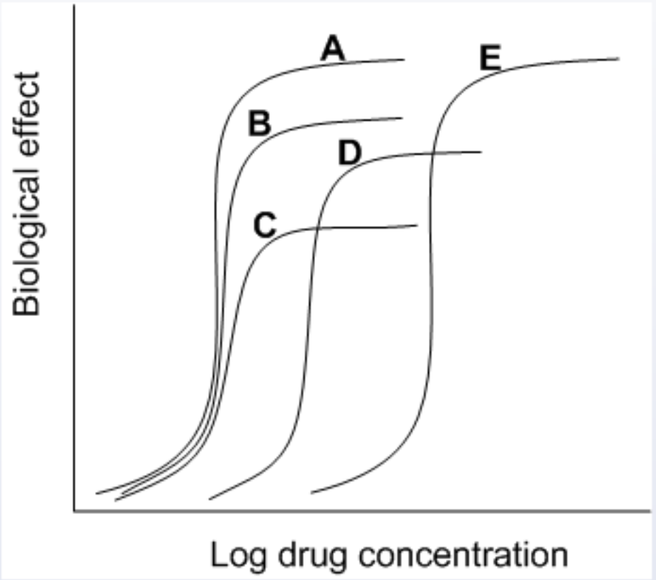
A group of investigators examined the effects of different muscarinic agonists and antagonists on the bladder musculature. The curves presented below were constructed after application of different agents. Curve A represents the effect of bethanechol, a pure cholinergic agonist.



Which of the curves most likely represents the effect of bethanechol after application of a reversible competitive antagonist?

- A. Curve A
- B. Curve B
- C. Curve C
- D. Curve D
- E. Curve E

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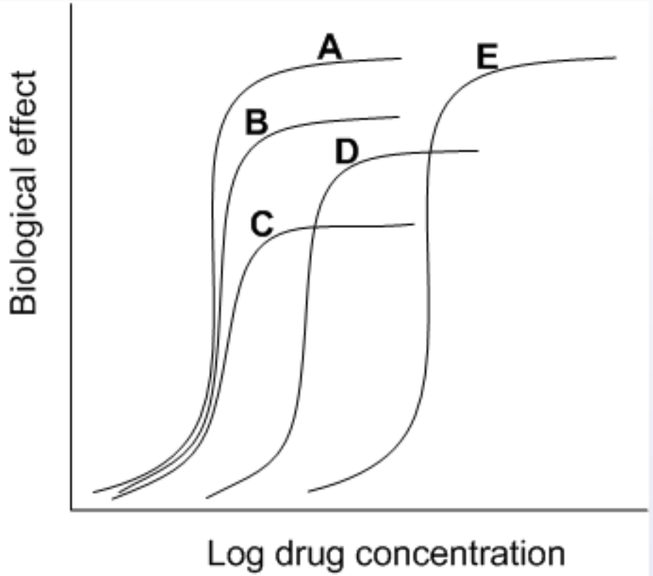

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- C. Curve C
- D. Curve D
- E. Curve E

Submit

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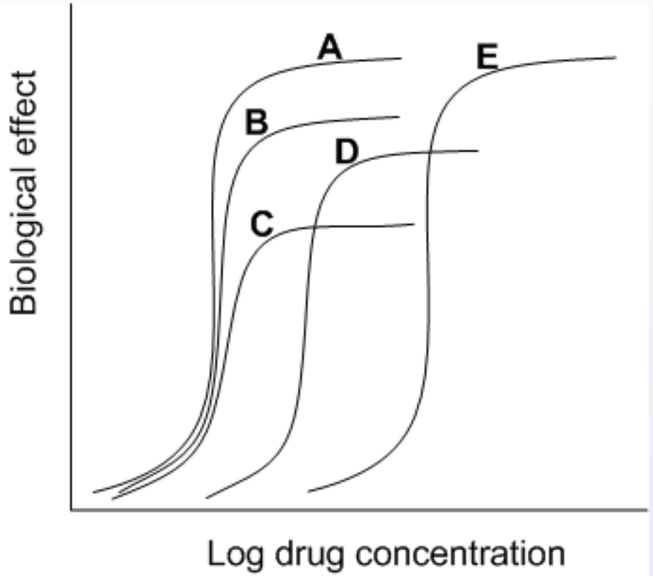

Which of the curves most likely represents the effect of bethanechol after application of a reversible competitive antagonist?

A. Curve A (0%)
B. Curve B (3%)
C. Curve C (9%)
D. Curve D (5%)
✓ E. Curve E (80%)

Omitted
Correct answer

80%
Answered correctly

04 secs
Time Spent

02/03/2020
Last Updated

Antagonists are agents that bind to but do not activate receptors. Antagonists can be either competitive or noncompetitive. Competitive antagonists bind to the exact same receptor binding sites as endogenous or exogenous agonists, thereby preventing agonist binding and activation of the receptor. Competitive antagonism can be reversible (ionic bond) or irreversible (covalent bond). The effect of a reversible competitive antagonist can be overcome by high concentrations of agonist, which cause displacement of the antagonist from the receptors by mass action.

Noncompetitive antagonists, on the other hand, bind to receptors at a site other than the primary agonist binding site, thereby causing a conformational (allosteric) change in the receptor protein that modifies the agonist binding site and prevents agonist binding. By binding to a different site than the agonist, noncompetitive antagonists are able to remain bound to the receptor even when high concentrations of agonist are present because the agonist is unable to displace noncompetitive antagonists from the receptor.

The question has asked how the curve for bethanechol **(Curve A)** would be affected by the introduction of a reversible competitive antagonist. A reversible competitive antagonist is expected to require higher doses of the full agonist (bethanechol) to be present to achieve the same effect at each point along the curve. If enough of the original substrate is added, the reaction can still reach the same maximum effect. Thus, the log dose-response curve for a full agonist combined with a reversible competitive antagonist will exhibit a parallel shift to the right in the log-dose response curve, with an increase in the ED_{50} and no change in the maximum effect (E_{max}).

(Choice A) Curve A is the dose-response curve for the original agonist drug in the absence of modifiers such as antagonists.

(Choices B and C) Both Curves B and C represent the effect of adding a noncompetitive antagonist to the agonist. Note that the ED_{50} is unchanged (i.e. the ED_{50} for Curves A, B and C occur at the exact same log drug concentration). This is a distinguishing characteristic of noncompetitive antagonism. The maximum effect (E_{max}) of Curves B and C are reduced because the noncompetitive antagonist has effectively reduced the number of receptors available for binding. The decrease in E_{max} will depend on the dose of noncompetitive antagonist present and is illustrated by the difference between Curves B and C, where a higher concentration of antagonist is present in Curve C than in Curve B.

(Choice D) Curve D illustrates a rightward shift in the dose-response relationship, but the shift is not a parallel shift because the shape of the curve differs from that of Curve A, with changes in both E_{max} and ED_{50}. This curve is not characteristic of any single antagonist effect and may be the result of adding multiple types of antagonists.

Educational Objective:

present because the agonist is unable to displace noncompetitive antagonists from the receptor.

The question has asked how the curve for bethanechol **(Curve A)** would be affected by the introduction of a reversible competitive antagonist. A reversible competitive antagonist is expected to require higher doses of the full agonist (bethanechol) to be present to achieve the same effect at each point along the curve. If enough of the original substrate is added, the reaction can still reach the same maximum effect. Thus, the log dose-response curve for a full agonist combined with a reversible competitive antagonist will exhibit a parallel shift to the right in the log-dose response curve, with an increase in the ED_{50} and no change in the maximum effect (E_{max}).

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Educational Objective:
The changes in the log dose-response curve expected for the effect of a reversible competitive antagonist added to a full agonist are: 1) a parallel shift to the right in the log-dose response curve, illustrating an increase in the ED_{50}, and 2) no change in the maximum effect (E_{max}).

* Competitive=change ED_{50}=shift right; noncompetitive=change E_{max}=shift down.

Pharmacology	General Principles	Dose response curves
Subject	System	Topic

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A novel antiretroviral medication, Drug X, is being developed for treating patients with HIV infection. Initial studies show a high rate of treatment failure due to continued viral proliferation in the brain. However, treatment success rates improve when Drug X is combined with an adjuvant agent. Data comparing the two medication regimens is shown in the table below.

	Drug X only	Drug X + adjuvant
Average cerebral spinal fluid (CSF) viral load (1 month)	1860 copies/mL	480 copies/mL
Average CSF viral load (6 months)	1640 copies/mL	undetectable
Average serum concentration of Drug X	550 ng/ml	560 ng/ml

Based on the data, the adjuvant agent most likely improves viral control through which of the following mechanisms?

A. Blocking first-pass metabolism

B. Decreasing cytochrome P450 metabolism

C. Diminishing blood flow to the choroid plexus

D. Inhibiting cellular efflux transporters

E. Reducing glomerular filtration of the drug

Submit

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Based on the data, the adjuvant agent most likely improves viral control through which of the following mechanisms?

A. Blocking first-pass metabolism (9%)

B. Decreasing cytochrome P450 metabolism (19%)

C. Diminishing blood flow to the choroid plexus (15%)

✓ D. Inhibiting cellular efflux transporters (50%)

E. Reducing glomerular filtration of the drug (4%)

Omitted
Correct answer
D

50%
Answered correctly

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Time Spent

02/18/2020
Last Updated

Explanation

Explanation

The study results show that the cerebral spinal fluid (CSF) viral load level remains elevated when subjects are treated with Drug X alone but becomes undetectable when Drug X is combined with the adjuvant agent. Because average serum levels are relatively equal between the 2 groups, it is likely that the adjuvant improves the efficacy of Drug X by increasing its ability to penetrate the **blood-brain barrier** (BBB).

Many drugs have a difficult time crossing the BBB due to the presence of specialized endothelial cells with very **tight intercellular junctions** that form a **physical barrier** separating the CNS from the circulation. In addition, multidrug transport proteins, particularly **p-glycoprotein**, are highly expressed on the luminal membrane of brain capillary endothelial cells. P-glycoprotein is an ATP-driven **efflux pump** that actively **removes a wide range of substrates** from cells, including many commonly prescribed drugs (eg, antibiotics, immunosuppressant agents, HIV protease inhibitors).

In HIV infection, poor penetration of antiretroviral medications allows the brain to act as an anatomical sanctuary where viral replication can proceed unchecked, facilitating the development of resistant strains. Methods of bypassing the BBB (eg, disruption of tight junctions, **p-glycoprotein inhibition**) can **improve drug delivery** to the CNS. P-glycoprotein transporters are also found on the apical surface of enterocytes and can limit drug bioavailability by pumping the drug back into the intestinal lumen. However, inhibition of p-glycoprotein can have a **variable effect on serum drug levels**, as increased bioavailability is often countered by increased drug distribution (eg, into the CSF or intracellular compartments).

(Choices A, B, and E) Reduced drug metabolism or decreased excretion could potentially improve drug efficacy by increasing average serum drug levels. However, in this experiment, serum drug levels increased by only 10 ng/ml (~2%) with coadministration of the adjuvant. This minimal increase in drug concentration is not representative of a significant change in drug metabolic/clearance parameters and is unlikely to lead to increased BBB penetration.

(Choice C) The choroid plexus is the site of CSF production and can function as an alternate entryway into the CNS. However, the excretion of a substance by the choroid plexus is directly dependent on choroidal blood flow; diminished blood flow would reduce the excretion of a particular substance into the CSF.

Educational objective:
P-glycoprotein is an efflux pump found on brain capillary endothelial cells (part of the blood-brain barrier) that inhibits a wide range of substrates from entering the brain. Inhibition of p-glycoprotein can improve drug delivery to the CNS.

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Pharmacology	General Principles	Volume of distribution
Subject	System	Topic

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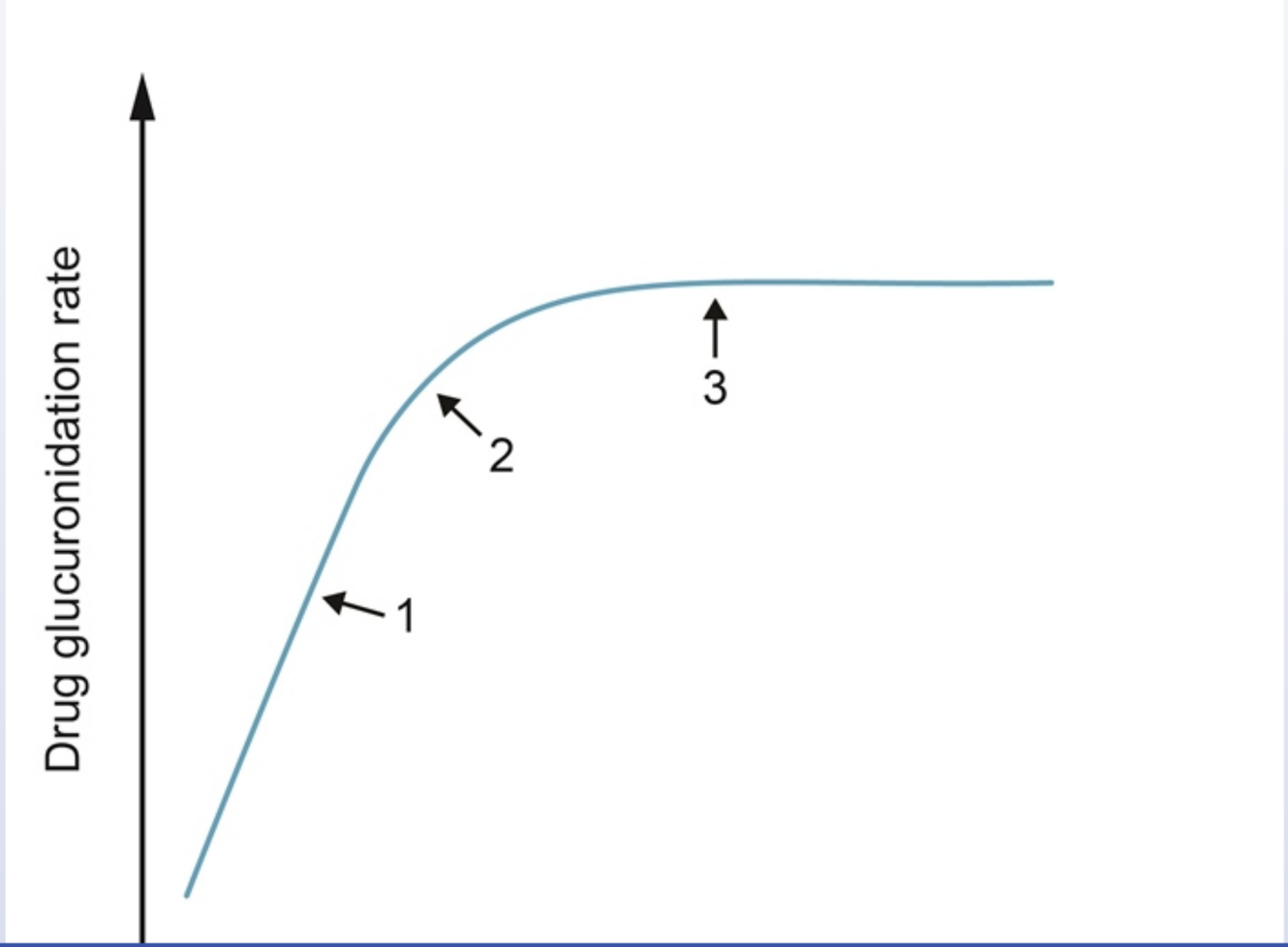
A large, multinational drug corporation conducts a phase I clinical trial to evaluate the safety profile and pharmacokinetic properties of a new drug designed to treat refractory epilepsy. Initial studies in animals showed that the drug undergoes extensive metabolism by the liver into glucuronidation byproducts that are primarily excreted by the kidneys. The curve below demonstrates the glucuronidation rate of the drug over a wide range of doses.



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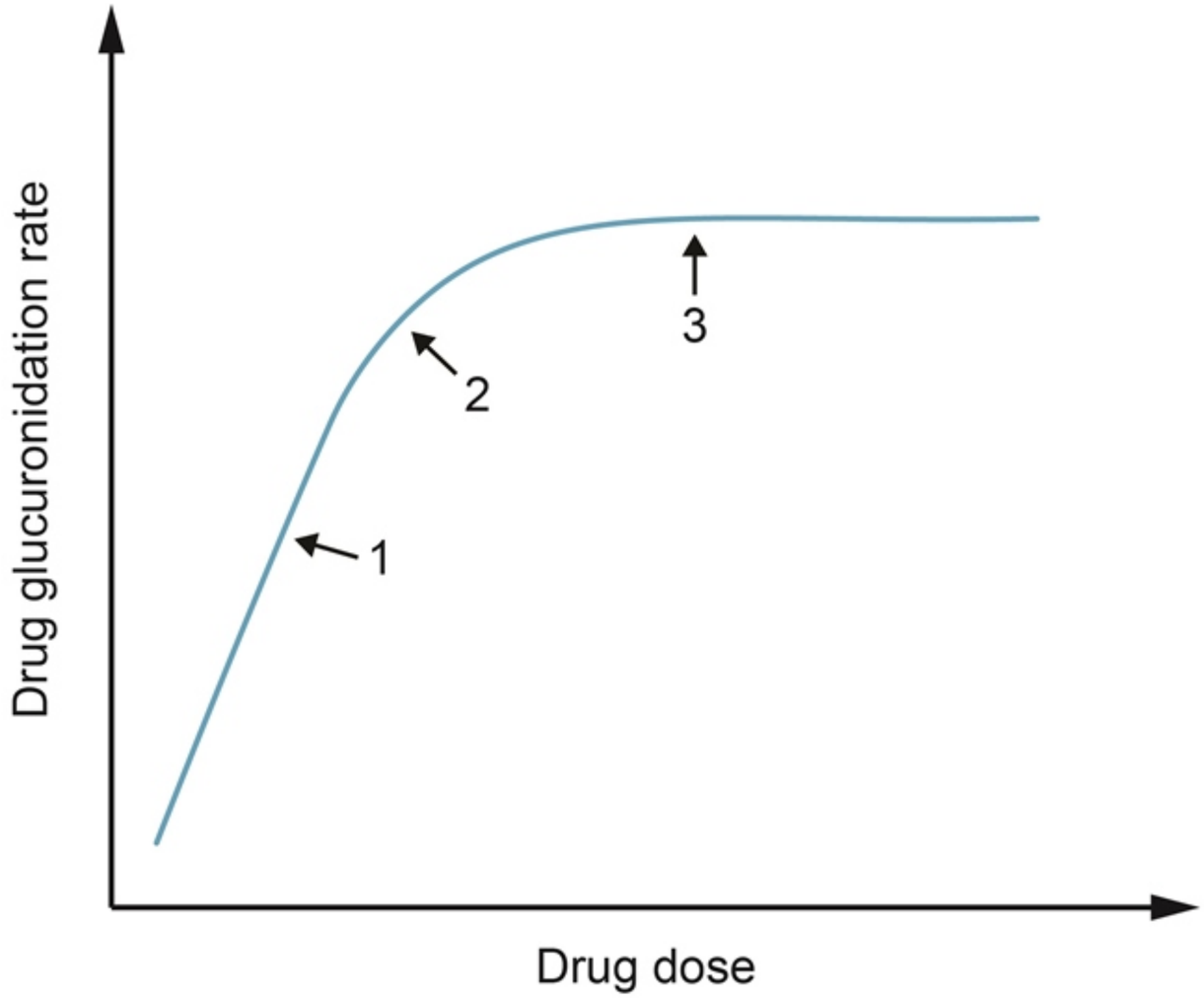

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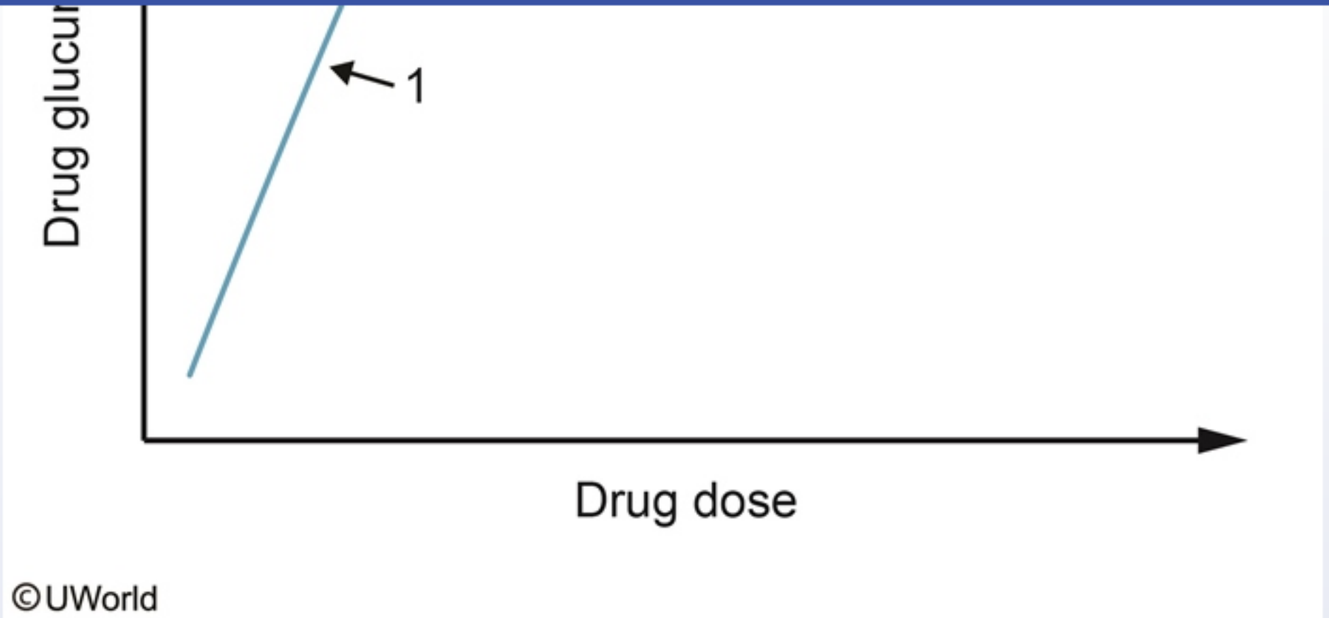

Which of the following is the most accurate statement about this drug's metabolism?

- A. A constant proportion of the drug is metabolized past point 3
- B. Bioavailability of the drug is highest at point 1
- C. Biotransformation of the drug ceases near point 2
- D. Metabolism begins to switch to zero-order kinetics near point 2
- E. The rate of drug metabolism is not dependent on dose before point 1

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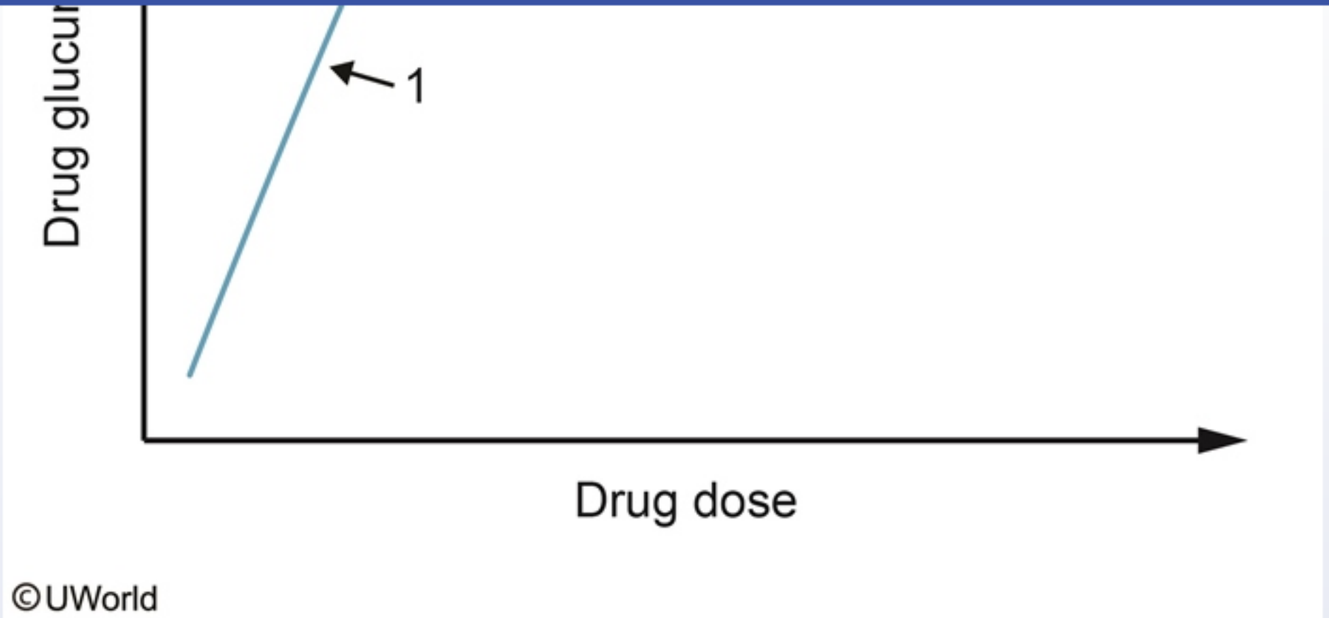

Which of the following is the most accurate statement about this drug's metabolism?

A. A constant proportion of the drug is metabolized past point 3 (37%)

B. Bioavailability of the drug is highest at point 1 (5%)

C. Biotransformation of the drug ceases near point 2 (5%)

✓ D. Metabolism begins to switch to zero-order kinetics near point 2 (47%)

E. The rate of drug metabolism is not dependent on dose before point 1 (3%)

Omitted
Correct answer

47%
Answered correctly

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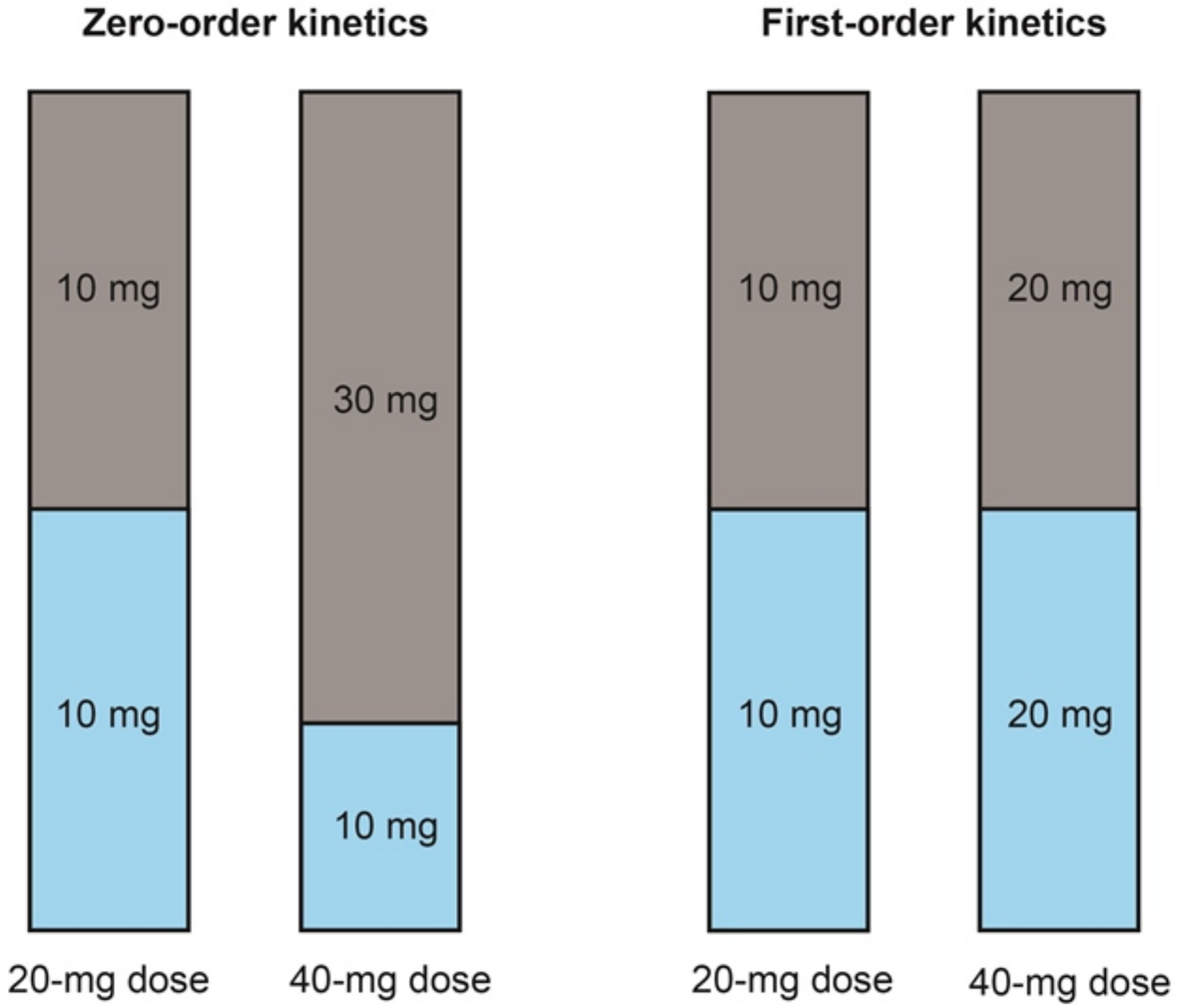
Zero- and first-order drug metabolism



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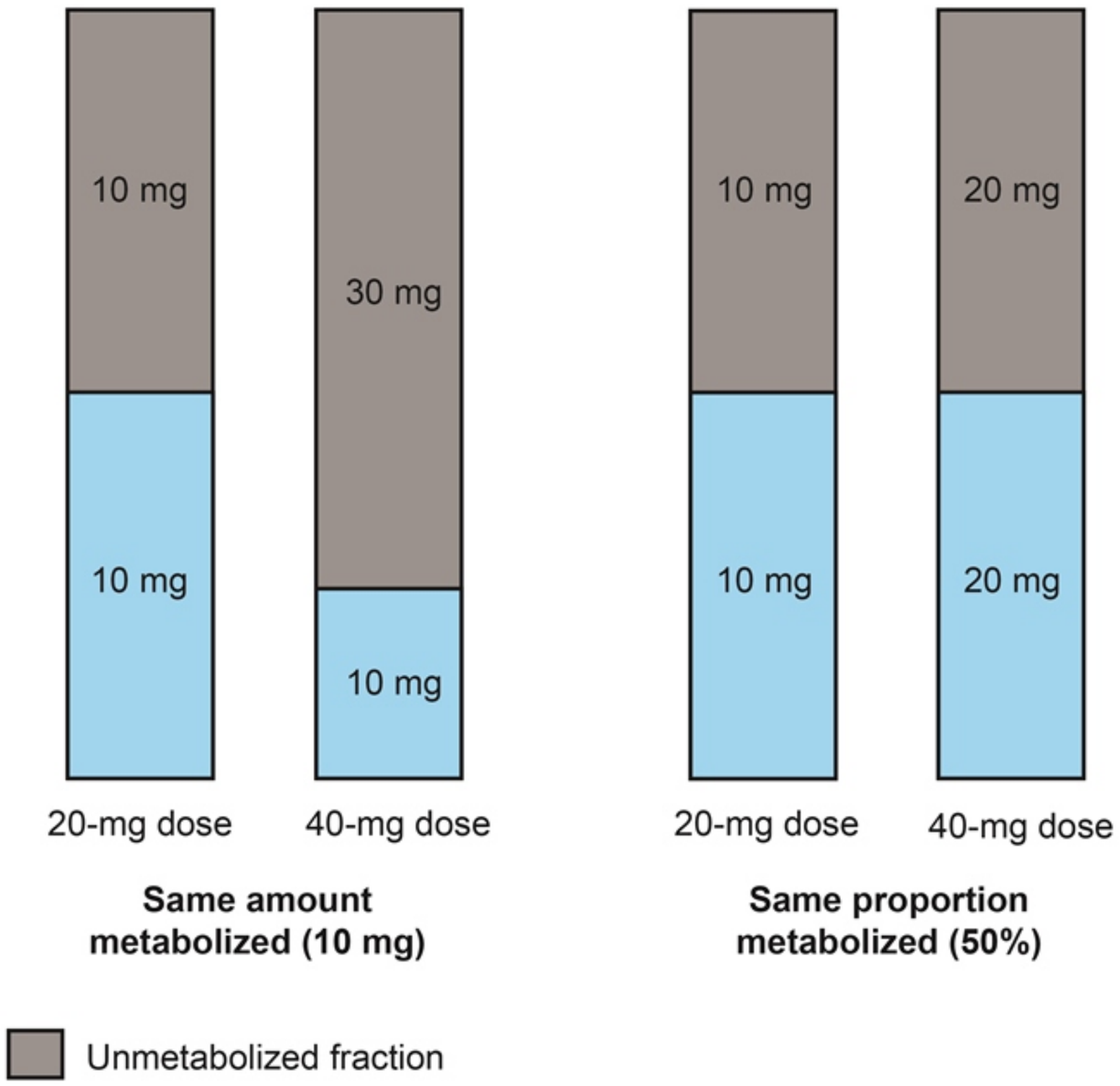

The drug under investigation is glucuronated by the liver into water-soluble byproducts that can then be excreted by the kidney. The graph above shows how the **rate of drug glucuronidation** changes with increasing drug doses. At lower doses, the quantity of drug-glucuronide formed is directly proportional to the dose administered (ie, as more of the drug is administered, more drug-glucuronide is produced). Because a **fixed proportion** of drug is converted to the metabolite, this early portion of the graph represents **first-order kinetics**.

As the active sites on glucuronosyltransferase become saturated, the drug-glucuronide rate does not continue to rise with increasing doses of the substrate drug. At this point (2 on the graph), the kinetics change from first- to **zero-order kinetics** and the graph levels out to a zero slope. With zero-order kinetics, **a constant amount** of drug is metabolized and eliminated per unit of time regardless of its concentration or dose.

Zero- and first-order kinetics can also be represented graphically by showing the decrease in drug concentration over time after a single dose. Zero-order metabolism is indicated by a straight line with negative slope (fixed amount eliminated per unit of time), whereas first-order kinetics manifest as an exponential decay curve (fixed proportion eliminated per unit of time).

(Choice A) After point 3, the curve remains flat, indicating that a constant amount of drug is metabolized per unit of time regardless of the dose. As higher doses are administered, the proportion that is converted to the metabolite becomes smaller (ie, the proportion metabolized is non-constant after point 3).

(Choice B) Bioavailability is the fraction of an administered drug that reaches the systemic circulation unchanged. It usually decreases with oral administration due to incomplete absorption and first-pass metabolism compared to parenteral administration. In this case, higher doses of the drug are likely to have greater bioavailability due to the saturation of hepatic metabolism.

(Choice C) At point 2, biotransformation (ie, metabolism) of the drug begins to switch from first-order to zero-order kinetics due to enzyme saturation. However, drug metabolism does not stop.

(Choice E) Before point 1, drug metabolism proceeds via first-order kinetics. Therefore, the drug metabolization rate increases as higher doses are administered.

Educational objective:
In first-order kinetics, a constant fraction (or proportion) of drug is metabolized per unit of time, so the amount metabolized changes based on the serum concentration. In zero-order kinetics, a constant amount of drug is metabolized per unit of time, independent of serum levels.

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The drug under investigation is glucuronated by the liver into water soluble byproducts that can then be excreted by the kidney. The graph above

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Pharmacology	General Principles	Drug metabolism and clearance
Subject	System	Topic

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A clinical trial is being conducted to evaluate the safety and efficacy of a novel therapy to treat refractory Crohn disease. The medication is a monoclonal antibody against the α4β7 integrin, which inhibits migration of T-lymphocytes into the intestinal parenchyma and produces a gut-selective anti-inflammatory effect. Patients who have active, moderate to severe Crohn disease and have failed conventional therapy are enrolled in the study. Many of these patients have renal or hepatic dysfunction, and some take other medications that affect cytochrome P450 enzymes. Which of the following is the most appropriate dose adjustment in this patient population to decrease drug toxicity?

A. Higher dose in patients taking cytochrome P450 inducers

B. Lower dose in patients with decreased glomerular filtration

C. Lower dose in patients with hepatocellular dysfunction

D. Lower dose in patients with renal tubular dysfunction

E. No dose adjustment necessary

Submit

A clinical trial is being conducted to evaluate the safety and efficacy of a novel therapy to treat refractory Crohn disease. The medication is a monoclonal antibody against the α4β7 integrin, which inhibits migration of T-lymphocytes into the intestinal parenchyma and produces a gut-selective anti-inflammatory effect. Patients who have active, moderate to severe Crohn disease and have failed conventional therapy are enrolled in the study. Many of these patients have renal or hepatic dysfunction, and some take other medications that affect cytochrome P450 enzymes. Which of the following is the most appropriate dose adjustment in this patient population to decrease drug toxicity?

- A. Higher dose in patients taking cytochrome P450 inducers (17%)
- B. Lower dose in patients with decreased glomerular filtration (21%)
- C. Lower dose in patients with hepatocellular dysfunction (21%)
- D. Lower dose in patients with renal tubular dysfunction (7%)
- ✓ E. No dose adjustment necessary (32%)

Omitted
Correct answer
E

32%
Answered correctly

02 secs
Time Spent

07/08/2020
Last Updated

Explanation

Monoclonal antibodies (mAbs) are used to treat a growing variety of malignant (eg, leukemia/lymphoma, melanoma) and autoimmune diseases (eg, Crohn disease, rheumatoid arthritis). The therapeutic effect of mAbs is achieved by binding to their target antigen in the plasma or on the cell surface and **blocking deleterious receptor interactions** or triggering a **cytotoxic immune response** against abnormal cells.

Because of their large molecular size, mAbs cannot be administered orally and must be given via intravenous or subcutaneous/intramuscular routes. Unlike most other drugs, mAbs are **not eliminated by hepatic or renal clearance**, but are instead removed from the body in 2 primary

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Because of their large molecular size, mAbs cannot be administered orally and must be given via intravenous or subcutaneous/intramuscular routes. Unlike most other drugs, mAbs are **not eliminated by hepatic or renal clearance**, but are instead removed from the body in 2 primary ways:

- Target-mediated drug clearance: mAbs directed against cell surface antigens undergo internalization (receptor-mediated endocytosis) upon binding to their targets, removing them from the circulation
- Nonspecific clearance: Immunoglobulins are constitutively taken up by reticuloendothelial macrophages (via binding to Fc receptors) and vascular endothelial cells (via pinocytosis)

Once internalized, immunoglobulins are **catabolized into amino acids** within lysosomes.

(Choices A and C) Many drugs undergo modifications by the cytochrome P450 system and subsequent conjugation reactions within hepatocytes that help facilitate excretion of the drug into the urine or bile. In contrast, immunoglobulins are not metabolized by these systems, but rather broken down by proteolytic enzymes.

(Choices B and D) Immunoglobulins are too large to undergo substantial filtration at the glomerular basement membrane and are not secreted by the renal tubules. Therefore, renal dysfunction does not significantly affect monoclonal antibody clearance.

Educational objective:
Monoclonal antibodies (mAbs) are not eliminated by hepatic or renal clearance. Therefore, no dose adjustment is necessary with impaired hepatic/renal function or use of cytochrome P450 inducers or inhibitors.

References

- Pharmacokinetics of monoclonal antibodies.
- Quantification of IgG monoclonal antibody clearance in tissues.

Pharmacology General Principles Biologic agents

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Pharmacology	General Principles	Biologic agents
Subject	System	Topic

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A new antibiotic developed for the treatment of infections caused by resistant gram-positive cocci has a volume of distribution of 11L. It is eliminated by first-order kinetics and has a half-life of 10 hours. If given by a continuous infusion, approximately how much time would it require for the drug to achieve a 95% plasma steady state concentration?

A. 10 hours

B. 20 hours

C. 30 hours

D. 40 hours

Submit

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A. 10 hours (7%)

B. 20 hours (11%)

C. 30 hours (13%)

✓ D. 40 hours (67%)

Omitted
Correct answer
D

67%
Answered correctly

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Time Spent

06/27/2020
Last Updated

Explanation

During continuous infusion of a drug metabolized by first-order kinetics (i.e. a constant fraction of the drug is eliminated per unit time), the steady state concentration is reached in 4 to 5 half-lives. Thus, it would take approximately 40 hours, or four times the half-life of 10 hours, for the drug in question to reach approximately 95% steady-state concentration.

Educational objective:
During continuous infusion of a drug metabolized by first-order kinetics, the steady state concentration is reached in 4 to 5 half-lives.

Pharmacology General Principles Serum drug levels and half-life

Three alpha-agonist drugs are tested as potential vasoconstrictors. The degree of vasoconstriction is determined by measuring the cross-sectional area of an isolated vessel after application of the drug. The following curves are obtained:

Which of the following is the best statement concerning the effects of these drugs?

A. Drug 1 has lower potency than Drug 2

B. Drug 2 has higher affinity for alpha-receptors than Drug 3

C. Drug 1 demonstrates the highest efficacy

D. Drug 2 and Drug 3 bind to different loci of alpha-receptors

E. Drug 2 and Drug 3 demonstrate a similar potency

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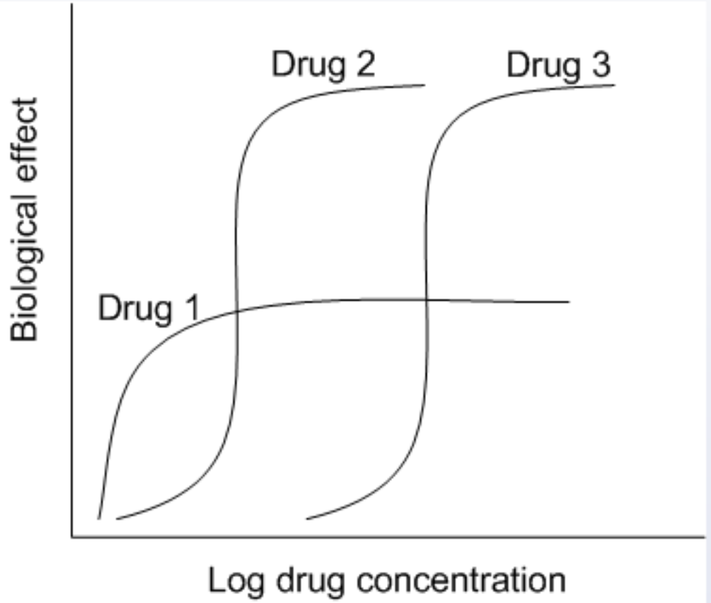

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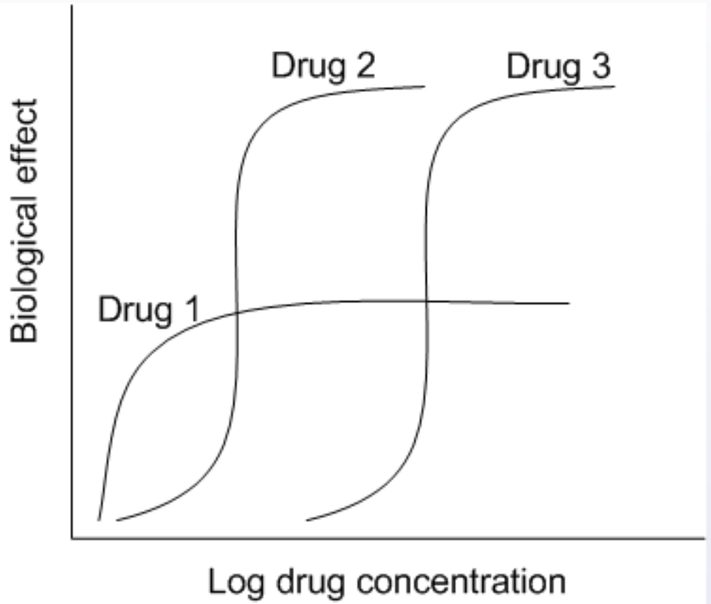

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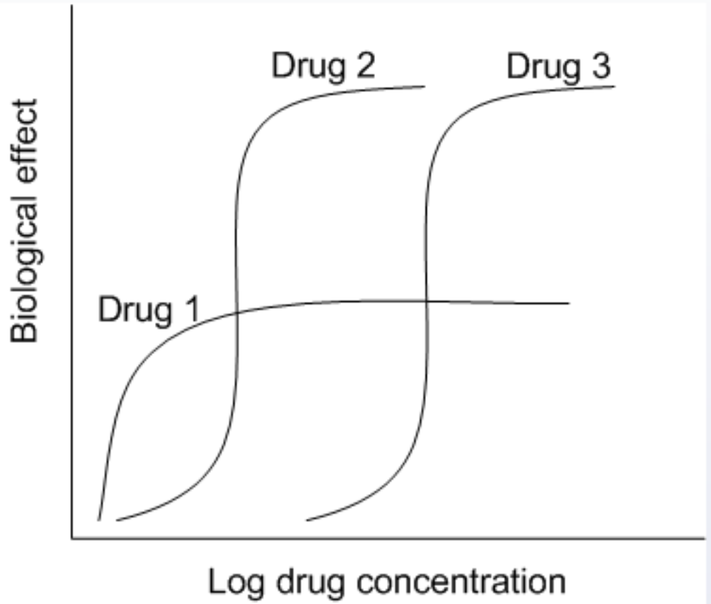

Which of the following is the best statement concerning the effects of these drugs?

A. Drug 1 has lower potency than Drug 2 (6%)

✓ B. Drug 2 has higher affinity for alpha-receptors than Drug 3 (76%)

C. Drug 1 demonstrates the highest efficacy (4%)

D. Drug 2 and Drug 3 bind to different loci of alpha-receptors (5%)

E. Drug 2 and Drug 3 demonstrate a similar potency (7%)

Omitted
Correct answer

76%
Answered correctly

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02/03/2020
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Efficacy and potency are terms that are commonly used and often confused. In pharmacology, efficacy refers to the intrinsic ability of a drug to elicit an effect, such as receptor activation or dilation of a vessel as described in the question stem. It is a measure of the maximum ceiling of activity [E_{max}] of a drug with respect to a particular pharmacodynamic end point. For example, loop diuretics such as furosemide or bumetanide will cause greater diuresis or natriuresis than any thiazide diuretic, irrespective of dose.

Potency, on the other hand, refers to the dose of drug that is required to produce a given effect. The potency of a drug is primarily affected by the affinity of the drug for its receptor and the amount of drug that is able to reach the target tissues Therefore, drugs that bind their receptors with a higher affinity or are better able to gain access to their target tissues will have greater potency. The potency of different agents can be compared by determining the dose of drug that is required to produce one-half (50%) of the maximum biological response. This dose is known as the ED_{50}. The lower the ED_{50} of a drug, the more potent it is. For example, among the thiazide diuretics, 25mg of hydrochlorothiazide and 5mg chlorthalidone produce similar drops in blood pressure (similar efficacy), but chlorthalidone requires a lower dose, or lower ED_{50}, than HCTZ to cause a similar effect (higher potency).

With respect to the question, drug 2 and drug 3 have similar maximum effects (efficacy). A much lower dose of drug 2 is required to produce the same effect as that seen with drug 3; therefore, drug 2 is more potent than drug 3 and has a lower ED_{50}. To achieve this higher potency, the binding of drug 2 to its receptors (affinity) must be higher than that of drug 3 **(Choice B)**, or drug 2 must be better able to reach its target (penetration) than drug 3.

(Choice A) Drug 1 has higher potency than Drug 2 because at low biological activity, it can cause the same effect with much lower concentrations of drug. However, it does not reach the same maximum effect as Drug 2.

(Choice C) Drug 1 demonstrates the lowest efficacy (ceiling of biological effect) of the three drugs graphed. Lower efficacy may be a result of partial agonism and other factors.

(Choice D) Drugs 2 and 3 exhibit a parallel shift in their relative biological effects exhibiting similar efficacy but different potency (The shapes of their graphs are identical, but at different dose ranges). Drug 3 may contain the same basic pharmocologic agent as Drug 2 but with a competitive antagonist mixed in; thus, the E_{max} is the same but the ED_{50} is higher. A competitive antagonist would bind to the same location as the original substance.

(Choice E) Drug 2 has a lower ED_{50} (greater potency) than drug 3. Both have equal efficacy

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Educational Objective:
Efficacy is a measure of the maximum pharmacodynamic effect achievable with a drug. Potency refers to the dose of drug that is required to produce a given effect. Drugs that bind their receptors with a higher affinity or are better able to gain access to their target tissues will have greater potency (lower ED_{50}).

Pharmacology	General Principles	Dose response curves
Subject	System	Topic

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A researcher is conducting a retrospective study on breast cancer recurrence. Records of a number of patients with hormone receptor-positive, early-stage breast cancer who received adjuvant therapy with tamoxifen were evaluated. Various clinical, demographic, and drug concentration data were analyzed. A comparison of patients who had disease recurrence with those who remained cancer free showed that some of the relapsed patients had lower serum concentrations of endoxifen and 4-hydroxytamoxifen, the active metabolites of tamoxifen. Which of the following is the most likely cause of the drug's ineffectiveness in this subset of patients?

A. Activating mutation affecting a downstream signal transducer

B. Decreased hepatic N-acetyltransferase activity

C. Deficiency of thiopurine methyltransferase enzyme

D. Overexpression of P-glycoprotein in the tumor cells

E. Polymorphism of a cytochrome P450 enzyme

Submit

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A. Activating mutation affecting a downstream signal transducer (6%)

B. Decreased hepatic N-acetyltransferase activity (15%)

C. Deficiency of thiopurine methyltransferase enzyme (3%)

D. Overexpression of P-glycoprotein in the tumor cells (10%)

✓ E. Polymorphism of a cytochrome P450 enzyme (63%)

Omitted
Correct answer
E

63%
Answered correctly

02 secs
Time Spent

04/26/2020
Last Updated

Explanation

Cytochrome P450 (CYP) enzymes are a group of heme-containing proteins that are responsible for the majority of **drug metabolism**, which occurs predominately in the liver. Various CYP subtypes exist, with CYP3A, CYP2D, and CYP2C as the most active subtypes involved in drug metabolism. These enzymes generally function to deactivate drugs and facilitate excretion from the body by improving water solubility. However, they also metabolize certain compounds to their active forms.

Polymorphisms may occur in the genes coding for these enzymes, altering their expression or activity. Three important phenotypes exist: **poor,**

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Polymorphisms may occur in the genes coding for these enzymes, altering their expression or activity. Three important phenotypes exist: **poor, intermediate, and rapid metabolizer**. Identifying these variations on an individual basis provides a framework for optimizing therapy, predicting treatment efficacy, and minimizing toxicity.

Tamoxifen, a selective estrogen receptor modulator used in the treatment of estrogen receptor-positive breast cancer, is a prodrug metabolized by CYP2D to its **active metabolite, endoxifen**. Patients with genetic polymorphisms resulting in poor CYP2D activity are exposed to decreased levels of the active metabolite and have a higher risk of disease relapse.

(Choice A) Activation of downstream signal transducer proteins, such as KRAS, leads to activation of transcription factors that promote cell growth. Mutations in the *KRAS* gene are associated with the development of colorectal and lung cancers.

(Choice B) Decreased activity of hepatic N-acetyltransferase results in a diminished ability to metabolize drugs such as isoniazid and sulfonamides, leading to an increased likelihood of toxicity.

(Choice C) Thiopurine methyltransferase is responsible for the metabolism of thiopurine compounds such as the immunosuppressive drug 6-mercaptopurine. Enzyme deficiency leads to increased drug toxicity.

(Choice D) P-glycoprotein is a cell membrane protein that drives efflux of a number of substances out of the cell. Overexpression of p-glycoprotein in tumor cells has been identified as a cause of multidrug resistance.

Educational objective:
Cytochrome P450 enzymes found in the liver are responsible for the majority of drug metabolism. Polymorphisms occurring in the genes coding for these enzymes result in various phenotypes that differ in their rates of metabolism; individual differences in phenotype alter treatment efficacy and drug toxicity.

References

- Clinically relevant genetic variations in drug metabolizing enzymes.

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References

- Clinically relevant genetic variations in drug metabolizing enzymes.
- Association between CYP2D6 polymorphisms and outcomes among women with early stage breast cancer treated with tamoxifen.

Pharmacology	General Principles	Pharmacogenomics
Subject	System	Topic

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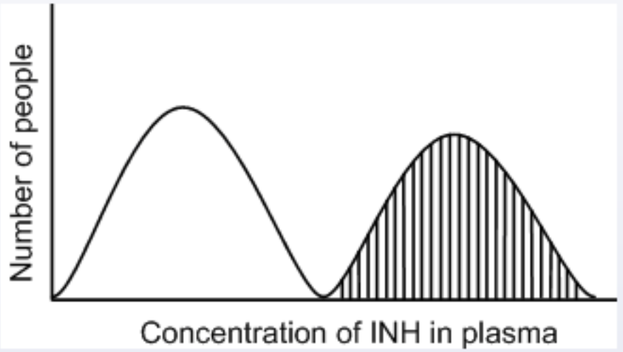
A group of investigators is performing an experiment designed to assess genetic variability in drug biotransformation. A fixed dose of isoniazid is given to a group of volunteers, and the plasma drug concentration is measured four hours following administration of the drug. The following distribution of plasma drug concentration in these subjects is obtained.



Variation of which of the following processes provides the best explanation for the shaded area of the curve?

A. Methylation
B. Glucuronidation
C. Hydrolysis
D. Acetylation
E. Amine oxidation

Submit

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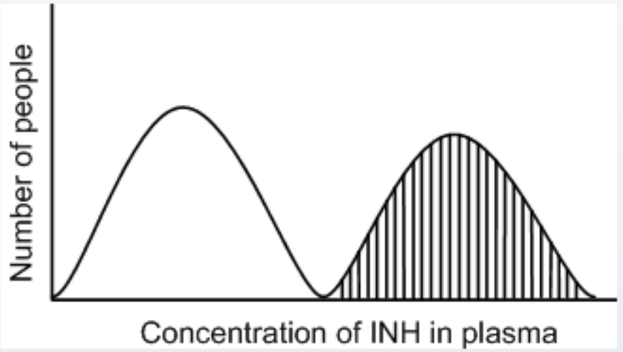

Variation of which of the following processes provides the best explanation for the shaded area of the curve?

A. Methylation (7%)
B. Glucuronidation (19%)
C. Hydrolysis (8%)
✓ D. Acetylation (59%)
E. Amine oxidation (5%)

Omitted
Correct answer
D

59%
Answered correctly

02 secs
Time Spent

02/03/2020
Last Updated

The rate and extent of drug metabolism normally varies from person to person. These slight interpersonal variations in the ability to metabolize drugs are typically reflected graphically by a unimodal distribution, usually in the shape of a bell curve, when plasma levels of drug are measured at a fixed time following a fixed dose of drug. This is the method that was used to generate the graph given in the question stem. With most drugs, the majority of people fall within one standard deviation and 95% of people fall within two standard deviations of the population mean of plasma concentration. A single peak in this type of graph indicates that the population being tested possesses a similar genetic drug metabolizing capacity.

A bimodal (discontinuous, polymorphic) curve, as shown in the question stem, results from the presence of two apparently distinct groups within the study population and suggests a pharmacogenetic polymorphism in drug metabolizing capacity. In other words, the two peaks indicate two sets of responders to the drug within the population: one that rapidly converts the drug into its metabolite (considered normals) and another that converts the drug slowly, leading to accumulation of the original drug in the plasma.

Isoniazid is metabolized by acetylation to N-acetyl-isoniazid in the hepatic microsomal system by the enzyme N-acetyl transferase and is subsequently excreted in the urine. The first and second peaks in the above graph represent fast and slow acetylators, respectively. Slow acetylators of isoniazid also metabolize (acetylate) dapsone, hydralazine, and procainamide slowly, causing accumulation of these drugs as well. Slow acetylators of these drugs are at increased risk of toxic effects, while fast acetylators may require much higher therapeutic doses to achieve a therapeutic effect.

(Choice A) Methylation is an important drug biotransformation method to consider when prescribing drugs such as azathioprine and 6-mercaptopurine, drugs used in the treatment of some inflammatory disorders of the bowel and skin.

(Choice B) Glucuronidation is a biotransformation pathway utilized for the metabolism of numerous drugs as well as endogenous substances such as bilirubin. No bimodality has been described with this pathway, but conditions such as Gilbert syndrome involve dysfunction of the glucuronyl transferase system that can lead to toxic accumulation of some drugs.

(Choice C) Hydrolysis occurs with enzymes such as esterases and amidases. Isoniazid is not metabolized by this pathway, and hydrolysis does not exhibit polymorphic metabolism.

(Choice E) Amine oxidation is usually undertaken by monoamine oxidases or by cytochrome oxidative deamination. Neither process metabolizes isoniazid nor exhibits bimodality.

Educational Objective:

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Educational Objective:
Isoniazid is metabolized by acetylation. The speed with which a patient is able to acetylate drugs depends on whether they are genetically "fast" or "slow" acetylators. The presence of fast and slow acetylators within the same population results in a bimodal distribution of the speed of isoniazid metabolism. Slow acetylators are at increased risk of adverse side effects.

Pharmacology	General Principles	Pharmacogenomics
Subject	System	Topic

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A new aminoglycoside antibiotic is developed that is believed to be particularly effective against *Pseudomonas*. The volume of distribution of the drug is measured in a group of volunteers and is determined to be 4.5 L. This new drug is most likely to have which of the following properties?

A. It has low molecular weight

B. It is lipophilic

C. It does not bind to albumin

D. It is highly charged

E. It has high oral bioavailability

Submit

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A. It has low molecular weight (4%)

B. It is lipophilic (28%)

C. It does not bind to albumin (13%)

✓ D. It is highly charged (39%)

E. It has high oral bioavailability (13%)

Omitted
Correct answer
D

39%
Answered correctly

02 secs
Time Spent

02/03/2020
Last Updated

Explanation

The volume of distribution (V_d) refers to a hypothetical volume of fluid into which the administered amount of drug would need to be uniformly distributed to produce the observed plasma concentration. The volume of distribution is determined by administering a given amount of drug by the intravenous route and subsequently measuring the initial plasma concentration of the drug. The formula is as follows:

V_d (L) = amount of drug given (mg) / plasma concentration of drug (mg/L)

The average total body water is approximately 41 liters. Of that, the extracellular fluid volume is about 14 L, or 1/3 of total body water. Within the extracellular fluid, the plasma volume is about 3 L, and interstitial fluid makes up the rest. Initially, the drug enters the plasma compartment by the IV route. If a drug has a large molecular weight, is bound extensively to plasma proteins, or is highly charged (hydrophilic), then the drug generally

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(Choice A) If the molecular weight of the drug is low, then the drug will tend to easily pass through endothelial junctions into the interstitial fluid, making the volume of distribution at least 14 liters. The Vd may be higher if the drug is also hydrophobic.

(Choice B) Lipophilic drugs tend to readily cross cell membranes and distribute widely outside the plasma and interstitial compartments. This tendency to collect within cells gives these drugs a high volume of distribution.

(Choice C) A drug with a V_d of 4.5 L, which is approximately the same as the plasma volume, is likely to be highly bound to plasma proteins such as albumin. Binding to plasma proteins tends to retain drug in the plasma compartment and prevent the diffusion of drug into the extravascular compartments. If this drug were not bound to albumin, it would be more likely to diffuse into the interstitium and a higher V_d would be expected.

(Choice E) Bioavailability is a measure of absorption and is unrelated to the distribution of a drug.

Educational Objective:
Characteristics of a drug such as high molecular weight, high plasma protein binding, high charge, and hydrophilicity tend to trap the drug in the plasma compartment resulting in a low V_d (3-5 L).

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Pharmacology	General Principles	Drug structure and properties
Subject	System	Topic

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A 31-year-old man comes to the office due to persistent nasal congestion and rhinorrhea. The patient has a history of allergic rhinitis and recently moved across the country to start a new job. His nasal symptoms worsened after the move, and he started using an over-the-counter intranasal decongestant spray that initially provided prompt relief. However, after a few days, he had to increase the frequency and number of sprays per nostril needed for adequate symptom control. On examination, the nasal turbinates are swollen and pale with a clear nasal discharge. Which of the following mechanisms is most likely responsible for this patient's increased medication use?

A. Accelerated drug metabolism

B. Decreased receptor affinity

C. Depletion of receptor-associated G proteins

D. Increased receptor internalization

E. Reduced parasympathetic activity

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- A. Accelerated drug metabolism (4%)
- B. Decreased receptor affinity (31%)
- C. Depletion of receptor-associated G proteins (12%)
- ✓ D. Increased receptor internalization (48%)
- E. Reduced parasympathetic activity (3%)

Omitted
Correct answer
D

48%
Answered correctly

03 secs
Time Spent

05/31/2020
Last Updated

Explanation

Example mechanisms of tachyphylaxis	
Adrenergic agonists	Receptor inactivation & internalization by arrestins
Indirect sympathomimetics	Depletion of catecholamines from nerve terminals

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Adrenergic agonists	Receptor inactivation & internalization by arrestins
Indirect sympathomimetics	Depletion of catecholamines from nerve terminals
Nitrates	Depletion of reduced thiols decreases mtALDH activity & NO production
Desmopressin (vWD)	Depletion of vWF from endothelial storage sites
Barbiturates	Induction of CYP450 enzymes

CYP450 = cytochrome P450; **mtALDH** = mitochondrial aldehyde dehydrogenase; **NO** = nitric oxide; **vWD** = von Willebrand disease; **vWF** = von Willebrand factor.

This patient has rhinitis medicamentosa due to the use of a nasal decongestant spray containing an **alpha-adrenergic agonist** (eg, oxymetazoline). Intranasal application of alpha agonists induces vasoconstriction of superficial blood vessels in the nasal mucosa, reducing rhinorrhea and congestion. Although these agents are highly effective for symptom control, use for more than a few days is associated with **rebound rhinitis** and dosage escalation due to **tachyphylaxis**.

Tolerance to alpha-adrenergic decongestants develops quickly due to **receptor internalization**. Both alpha- and beta-adrenergic receptors undergo a conformational change on ligand binding, allowing them to activate heterotrimeric G proteins involved in signal transduction. However, the change in conformation also results in the binding of **arrestin**, a protein that prevents further G protein activation and links the receptor complex to clathrin, facilitating receptor endocytosis and depletion from the cell surface.

As alpha-adrenergic receptors become increasingly scarce along the blood vessels of the nasal mucosa, the release of endogenous catecholamines is no longer sufficient to provide adequate vasoconstrictive stimulation. The resulting congestion/rhinorrhea can be relieved only with **increasing doses** of exogenous alpha agonists. Treatment involves **cessation** of the culprit decongestant, sometimes with use of intranasal corticosteroids to relieve severe symptoms.

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(Choice B) Decreased receptor affinity due to intracellular domain modification (eg, phosphorylation) can play a role in receptor desensitization. However, desensitization of adrenergic receptors is better explained by the decoupling of G proteins (which are blocked by arrestins) and subsequent receptor internalization.

(Choice C) Tolerance to adrenergic agonists develops due to the binding of arrestins to stimulated adrenergic receptors, preventing G proteins from interacting with the receptor. G proteins themselves do not become depleted during this process.

(Choice E) Parasympathetic stimulation of the nasal mucosa causes vasodilation, increases plasma extravasation, and stimulates glandular mucous secretion. Patients with rhinitis medicamentosa have increased parasympathetic tone (physiologic antagonism) that contributes to the congestion/rhinorrhea.

Educational objective:
Activation of adrenergic receptors results in arrestin binding and receptor internalization. This effect is responsible for the tolerance effect seen with alpha-adrenergic (eg, decongestants, vasopressors) and beta-adrenergic (eg, bronchodilators) agonists.

undergo a conformational change on ligand binding, allowing them to activate heterotrimeric G proteins involved in signal transduction. However, the change in conformation also results in the binding of **arrestin**, a protein that prevents further G protein activation and links the receptor complex to clathrin, facilitating receptor endocytosis and depletion from the cell surface.

As alpha-adrenergic receptors become increasingly scarce along the blood vessels of the nasal mucosa, the release of endogenous catecholamines is no longer sufficient to provide adequate vasoconstrictive stimulation. The resulting congestion/rhinorrhea can be relieved only with **increasing doses** of exogenous alpha agonists. Treatment involves **cessation** of the culprit decongestant, sometimes with use of intranasal corticosteroids to relieve severe symptoms.

(Choice A) Accelerated drug metabolism can lead to tolerance when a substance induces the enzymes responsible for its degradation (ie, cytochromes P450). This mechanism is responsible for the tolerance seen with ethanol and barbiturates.

(Choice B) Decreased receptor affinity due to intracellular domain modification (eg, phosphorylation) can play a role in receptor desensitization. However, desensitization of adrenergic receptors is better explained by the decoupling of G proteins (which are blocked by arrestins) and subsequent receptor internalization.

(Choice C) Tolerance to adrenergic agonists develops due to the binding of arrestins to stimulated adrenergic receptors, preventing G proteins from interacting with the receptor. G proteins themselves do not become depleted during this process.

(Choice E) Parasympathetic stimulation of the nasal mucosa causes vasodilation, increases plasma extravasation, and stimulates glandular mucous secretion. Patients with rhinitis medicamentosa have increased parasympathetic tone (physiologic antagonism) that contributes to the congestion/rhinorrhea.

Educational objective:
Activation of adrenergic receptors results in arrestin binding and receptor internalization. This effect is responsible for the tolerance effect seen with alpha-adrenergic (eg, decongestants, vasopressors) and beta-adrenergic (eg, bronchodilators) agonists.

Pharmacology	General Principles	Signal transduction
Subject	System	Topic

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A clinical trial is conducted to assess the effectiveness of a novel formulation of cisplatin for treating advanced non–small cell lung cancer. Study participants are randomly assigned to 2 different cisplatin-based chemotherapy regimens. Subjects in the control arm are administered conventional cisplatin chemotherapy, whereas those in the experimental arm are given a formulation of cisplatin encapsulated in liposomes coated with anti–epidermal growth factor receptor (EGFR) antibodies. Patients in the experimental group are found to have a statistically significant decrease in residual tumor burden compared with those in the control group. The incidence of adverse effects was also lower in the experimental group. Compared to conventional cisplatin chemotherapy, the new formulation is most likely to have which of the following effects?

A. Decreased drug efflux from tumor cells

B. Enhanced cytotoxic T-cell response

C. Increased penetration through dense desmoplasia

D. Inhibition of tumor-induced angiogenesis

E. Selective drug uptake by cancer cells

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A. Decreased drug efflux from tumor cells (4%)

B. Enhanced cytotoxic T-cell response (5%)

C. Increased penetration through dense desmoplasia (9%)

D. Inhibition of tumor-induced angiogenesis (31%)

✓ E. Selective drug uptake by cancer cells (48%)

Omitted
Correct answer
E

48%
Answered correctly

02 secs
Time Spent

06/12/2020
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Explanation

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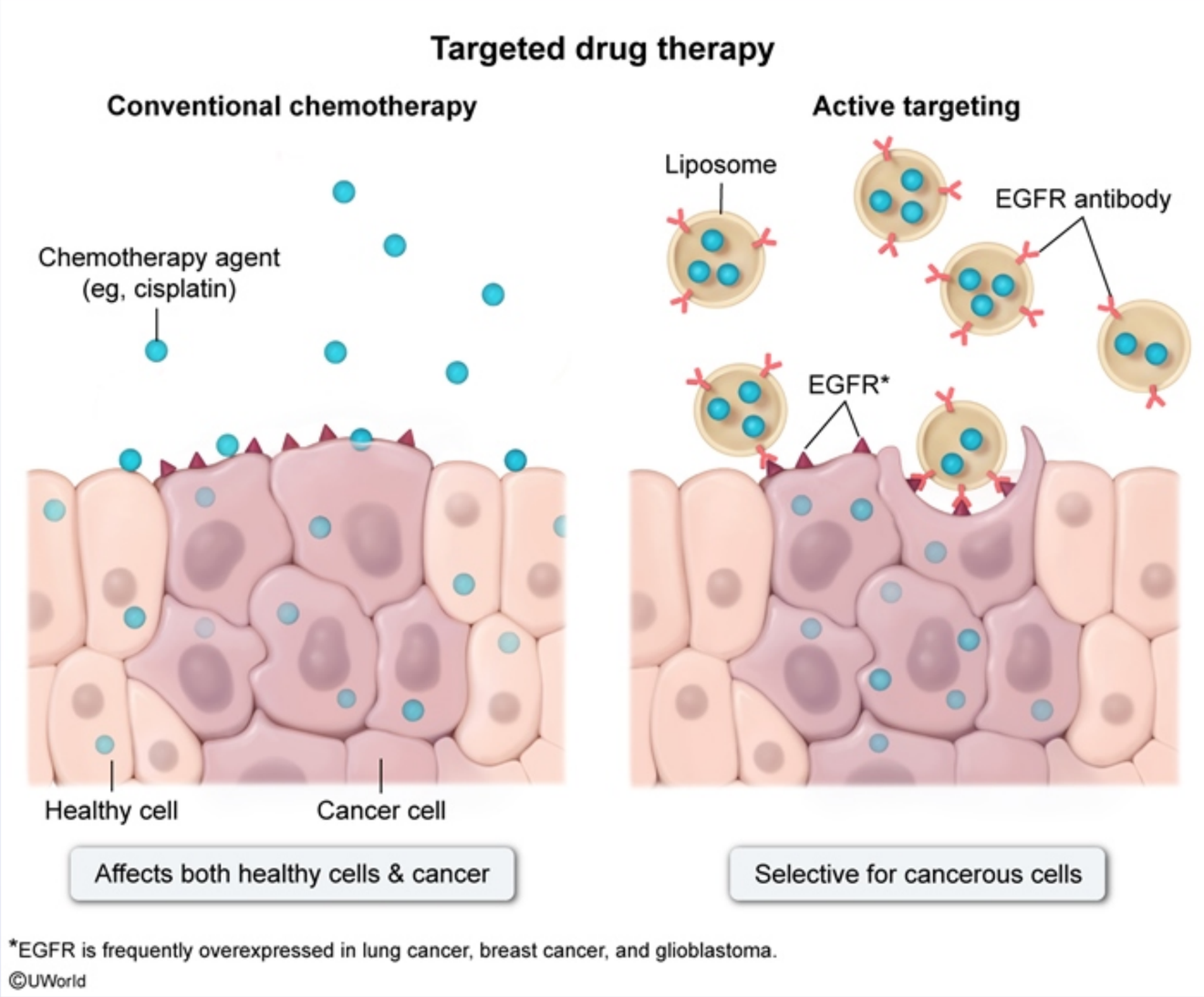

Platinum-based chemotherapy agents (eg, cisplatin) are widely used as a first-line treatment for many solid tumors, including non–small cell lung

Platinum-based chemotherapy agents (eg, cisplatin) are widely used as a first-line treatment for many solid tumors, including non–small cell lung cancer. These agents disrupt DNA replication and have substantial cytotoxicity against rapidly proliferating cells. Despite their efficacy in killing tumor cells, their use is limited by severe adverse effects (eg, nephrotoxicity, ototoxicity, myelosuppression) that occur due to accumulation within normal tissues (ie, off-target effects).

Methods that provide **targeted delivery** to the tumor site can help **minimize toxicity** and **optimize drug response**. In this example, cisplatin is encapsulated in liposomes, forming a nanoparticle cage that traps the drug and limits its interaction with normal cells. The addition of anti–epidermal growth factor receptor **(anti-EGFR) antibodies** on the liposome surface results in an **antibody-drug conjugate**, allowing the encapsulated drug complex to **selectively bind to tumor cells** expressing high levels of EGFR, which is often overexpressed in non–small cell lung cancer. Once bound, the antibody-drug complex is internalized and degraded, releasing the free drug into the cytoplasm and causing targeted cell death.

(Choice A) Overexpression of drug efflux pumps (eg, P-glycoprotein) by cancer cells is a major cause of chemotherapy resistance. Efflux pump inhibitors can decrease drug excretion from tumor cells and potentiate the effects of chemotherapeutic agents.

(Choice B) Many cancers create an immunosuppressive microenvironment that prevents the immune system from effectively killing tumor cells. An enhanced cytotoxic T-cell response against tumor cells occurs with the use of immune checkpoint inhibitors (eg, PD-1 or CTLA-4 receptor inhibitors) that help prevent T-cell exhaustion.

(Choice C) Desmoplasia (ie, reactive growth of fibrous connective tissue) occurs in response to certain tumors (eg, breast, pancreatic carcinoma). The dense fibrotic tissue acts as a molecular sieve, decreasing the penetration of chemotherapeutic agents. Chemoresistance is more likely to occur with larger drug complexes; in this case, the new liposomal formulation will be much larger than individual cisplatin molecules, resulting in decreased desmoplastic penetration.

(Choice D) Increased expression of vascular endothelial growth factor (VEGF) within tumors stimulates blood vessel growth, facilitating tumor expansion and increasing the potential for metastasis. Anti-VEGF antibodies (eg, bevacizumab) bind VEGF and inhibit tumor-induced angiogenesis. Although EGFR stimulation also plays a role in angiogenesis, in this case, the anti-EFGR antibodies are used for targeting purposes and may not necessary inhibit the EFGR receptor (antibodies can be stimulatory, inhibitory, or have no signaling effect depending on the attachment site).

Educational objective:

epidermal growth factor receptor **(anti-EGFR) antibodies** on the liposome surface results in an **antibody-drug conjugate**, allowing the encapsulated drug complex to **selectively bind to tumor cells** expressing high levels of EGFR, which is often overexpressed in non–small cell lung cancer. Once bound, the antibody-drug complex is internalized and degraded, releasing the free drug into the cytoplasm and causing targeted cell death.

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Educational objective:
Antibody-drug conjugates improve drug efficacy and minimize toxicity by allowing conventional chemotherapeutic agents (eg, cisplatin) to selectively target and kill cancer cells while sparing healthy cells (ie, targeted delivery).

Pharmacology	General Principles	Drug structure and properties
Subject	System	Topic

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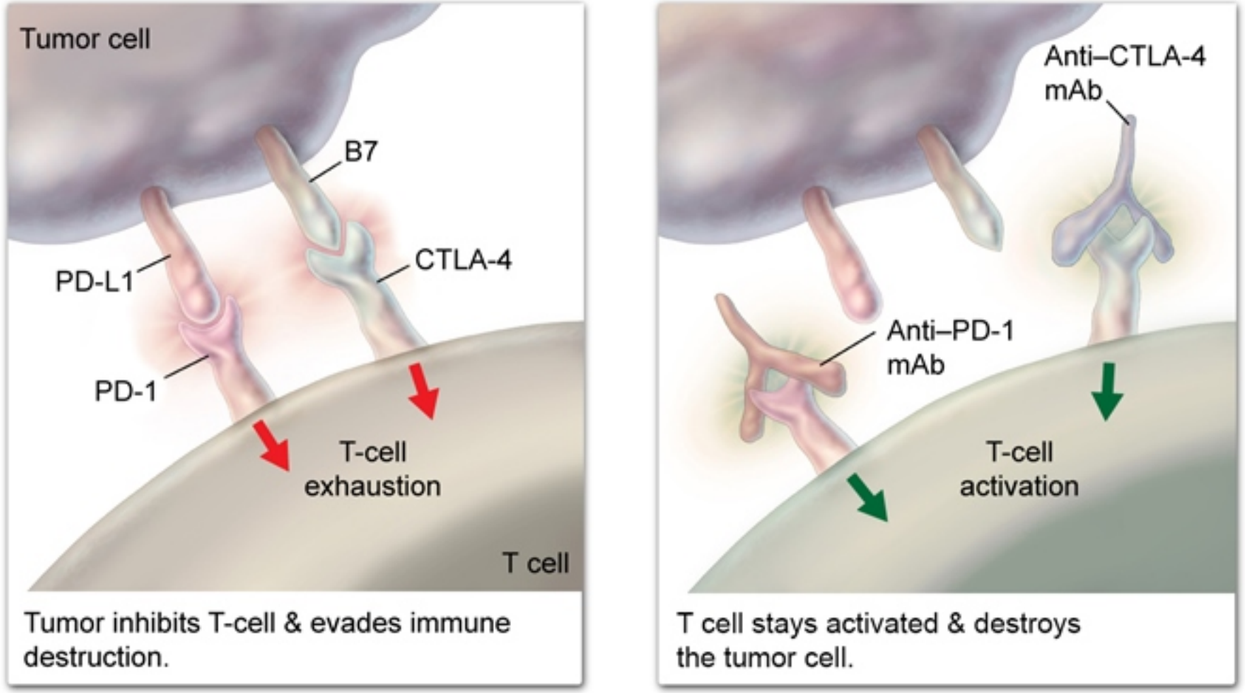
Cancer immunotherapy: anti–PD-1 & anti–CTLA-4 antibodies



CTLA-4 = cytotoxic T-lymphocyte–associated protein 4; **mAb** = monoclonal antibody;
PD-1 = programmed death receptor-1; **PD-L1** = programmed death ligand-1.
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encapsulated drug complex to **selectively bind to tumor cells** expressing high levels of EGFR, which is often overexpressed in non–small cell lung cancer. Once bound, the antibody-drug complex is internalized and degraded, releasing the free drug into the cytoplasm and causing targeted cell death.

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Pharmacology	General Principles	Drug structure and properties
Subject	System	Topic

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A 52-year-old man comes to the office for an annual preventive visit. He has a history of seasonal allergies, and has recently started taking a medication that has improved his runny nose, sneezing, and watery eyes. Medical history is remarkable for diet-controlled type 2 diabetes mellitus and eczema. He is not on any other medications. He does not use tobacco, alcohol, or illicit drugs. Examination shows a well-appearing man with flushed cheeks and dilated pupils. This patient's physical examination findings are best explained by which of the following mechanisms?

A. Antagonism of H1 receptors

B. Antagonism of H2 receptors

C. Antagonism of muscarinic receptors

D. Antagonism of nicotinic receptors

E. Stimulation of alpha-1 adrenoreceptors

Submit

A 52-year-old man comes to the office for an annual preventive visit. He has a history of seasonal allergies, and has recently started taking a medication that has improved his runny nose, sneezing, and watery eyes. Medical history is remarkable for diet-controlled type 2 diabetes mellitus and eczema. He is not on any other medications. He does not use tobacco, alcohol, or illicit drugs. Examination shows a well-appearing man with flushed cheeks and dilated pupils. This patient's physical examination findings are best explained by which of the following mechanisms?

- A. Antagonism of H1 receptors (18%)
- B. Antagonism of H2 receptors (4%)
- ✓ C. Antagonism of muscarinic receptors (57%)
- D. Antagonism of nicotinic receptors (1%)
- E. Stimulation of alpha-1 adrenoreceptors (17%)

Omitted
Correct answer
C

57%
Answered correctly

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06/13/2020
Last Updated

Explanation

Anticholinergic toxicity	
Symptom	**Mechanism**
"Hot as a hare" ↑ Body temperature	↓ Sweating leads to ↓ heat dissipation

Anticholinergic toxicity

Symptom	Mechanism
"Hot as a hare" ↑ Body temperature	↓ Sweating leads to ↓ heat dissipation
"Dry as a bone" ↓ Secretions (eg, mucous membranes, sweat glands)	↓ Glandular secretion & smooth muscle contraction
"Red as a beet" Flushed skin	Superficial vasodilation from ↑ body heat
"Blind as a bat" Cycloplegia, mydriasis	Paralysis of ciliary muscle & iris sphincter
"Mad as a hatter" Altered mental status	Permeates blood-brain barrier & affects CNS pathways
"Full as a flask" Urinary retention Constipation	↓ Detrusor contraction & ↓ internal urethral sphincter relaxation ↓ Intestinal smooth muscle contraction
"Fast as a fiddle" Tachycardia	↓ Vagal tone at the sinoatrial node

This patient is likely taking a **first-generation antihistamine** (eg, diphenhydramine), which are commonly used for treating environmental allergies and mast cell-related disorders. First-generation antihistamines are nonspecific and act as **antagonists** to multiple receptors, including the **muscarinic acetylcholine receptor**. This leads to **anticholinergic** effects (eg, fever, urinary retention, decreased sweating, altered mental status). In this patient, the flushing is likely a compensatory response to dissipate excess body heat due to decreased sweating, and the pupillary dilation is due to inhibition of the iris sphincter.

Although commonly described as H1 receptor antagonists, antihistamines are actually inverse agonists that stabilize the receptor in the inactive

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Tachycardia	↓ Vagal tone at the sinoatrial node

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Although commonly described as H1 receptor antagonists, antihistamines are actually inverse agonists that stabilize the receptor in the inactive state. H1 receptors are found in the vascular endothelium and bronchial smooth muscle, where they mediate vascular permeability and bronchoconstriction, as well as in the central nervous system where they are involved in alertness. Antihistaminic effects relieve nasal congestion, rhinorrhea, sneezing, and itching. First-generation antihistamines cross the blood-brain barrier and cause sedation. By contrast, second-generation antihistamines (eg, loratadine) are more specific to the histamine H1 receptor and have less permeability through the blood-brain barrier; they are generally less effective than first-generation antihistamines but have significantly fewer side effects.

(Choice A) Flushing and mydriasis are due to antagonism of the cholinergic receptor, not the H1 receptor.

(Choice B) H2 receptors are found on parietal cells in the gastric mucosa. H2 antagonists block gastric acid secretion by parietal cells.

(Choice D) Nicotinic cholinergic receptors are found in sympathetic and parasympathetic ganglia and on skeletal muscle cells at the neuromuscular junction. Nicotinic receptor antagonists (eg, rocuronium) are used to induce paralysis in preparation for surgery or endotracheal intubation. Adverse effects include hemodynamic instability (eg, hypotension) and respiratory insufficiency.

(Choice E) Alpha-1 adrenoreceptors are located on smooth muscle and neurons. Activation of these receptors increases smooth muscle tone of the iris dilator (causing mydriasis) and blood vessels (causing vasoconstriction); alpha-1 adrenergic agonists (eg, phenylephrine, oxymetazoline) can be used in patients with allergic rhinitis because their vasoconstrictive action reduces nasal congestion. However, vasoconstriction inhibits flushing.

Educational objective:
First-generation antihistamines are nonspecific and interact with multiple receptors, including the muscarinic receptor. This leads to anticholinergic effects (eg, fever, flushing, mydriasis, urinary retention, tachycardia, altered mental status).

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Pharmacology	General Principles	Allergic rhinitis
Subject	System	Topic

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A 35-year-old man comes to the emergency department due to acute onset coffee-ground emesis and lightheadedness. Three weeks ago, he developed lower back pain with stiffness and was started on naproxen and cyclobenzaprine. Past medical history is notable for moderate persistent asthma, hepatitis C, and HIV. His last CD4 count was 550/mm^3. The patient has a remote history of intravenous drug use but currently does not use any illicit drugs. He has an allergy to penicillin that causes a rash and pruritus. Upper gastrointestinal endoscopy reveals gastric mucosal erythema and erosions. Which of the following best explains this patient's current symptoms?

A. Exaggerated drug sensitivity
B. Idiosyncratic drug reaction
C. Immunologic drug reaction
D. Predictable drug reaction
E. Pseudoallergic drug reaction

Submit

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- A. Exaggerated drug sensitivity (14%)
- B. Idiosyncratic drug reaction (9%)
- C. Immunologic drug reaction (7%)
- ✓ D. Predictable drug reaction (65%)
- E. Pseudoallergic drug reaction (3%)

Omitted
Correct answer
D

65%
Answered correctly

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06/09/2020
Last Updated

Explanation

Drug adverse effects		
	Pharmacologic	• Orthostatic hypotension with alpha-1 blockade • Bradycardia with beta blockade • Gastritis with cyclooxygenase inhibition

Drug adverse effects		
Predictable	Pharmacologic	• Orthostatic hypotension with alpha-1 blockade • Bradycardia with beta blockade • Gastritis with cyclooxygenase inhibition • Nausea with many drugs (numerous mechanisms)
	Secondary (indirect)	• Oral thrush or *Clostridioides* (formerly *Clostridium*) *difficile* colitis with antibiotics • Phototoxicity with doxycycline
Unpredictable*	Immunologic	• Hypersensitivity (eg, anaphylaxis, serum sickness) • Drug-induced lupus, SJS/TEN
	Nonimmunologic	• Red man syndrome with vancomycin (pseudoallergy) • Hemolysis with sulfa drugs (G6PD) • Exaggerated azathioprine sensitivity (TPMT deficiency)

*Unpredictable adverse effects are usually driven by patient-specific genetics.

G6PD = glucose-6-phosphate deficiency; **SJS/TEN** = Stevens-Johnson syndrome/toxic epidermal necrolysis; **TPMT** = thiopurine methyltransferase.

This patient has acute **upper gastrointestinal (GI) hemorrhage**, which is likely an adverse reaction to his nonsteroidal anti-inflammatory drug (NSAID). **Cyclooxygenase** (COX) catalyzes the rate-limiting step in the conversion of arachidonic acid to prostaglandins, prostacyclin, and thromboxane. COX enzymes are involved in mediating inflammation but are also required for housekeeping functions (eg, platelet aggregation, gastric mucosal protection). COX enzymes are **inhibited by NSAIDs** such as naproxen. As a result, NSAIDs can cause **impairment** of prostaglandin-dependent **GI mucosal protection**, leading to mucosal erythema, erosions, and ulceration. Upper GI symptoms can occur within the first 24 hours of starting an NSAID, and changes to the mucosa can be seen within the first week.

Most adverse drug reactions are predictable due to the known pharmacologic properties of the drug and usually occur after extended drug exposure. Unpredictable reactions are less common and occur due to immune processes or other mechanisms. In this case, upper GI bleeding due to an NSAID is a well-known and **predictable** adverse event.

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(Choice A) Exaggerated drug sensitivity refers to adverse reactions that occur due to known pharmacologic actions of the drug but at a lower dose than expected (eg, due to altered metabolism or increased end-organ susceptibility). Patients with deficiency of thiopurine methyltransferase, an enzyme that metabolizes azathioprine, are more likely to experience adverse effects of the drug.

(Choice B) An idiosyncratic drug reaction is an unpredictable reaction due to genetic differences or complex metabolic interactions in certain patients. The use of trimethoprim-sulfamethoxazole in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency can lead to oxidative cellular injury and nonimmune hemolytic anemia.

(Choice C) Immunologic drug reactions (drug allergies) are unpredictable antibody or T cell-mediated responses to medications. This patient's history of rash and pruritus with penicillin likely represents IgE-mediated type I hypersensitivity.

(Choice E) Pseudoallergic drug reactions mimic immunologic reactions but occur via a nonimmunologic mechanism (eg, direct immune cell activation, inhibited prostaglandin synthesis). Vancomycin, opiates, and radioiodine contrast can directly activate mast cells to cause a pseudoallergic reaction that closely mimics IgE-mediated type I hypersensitivity.

Educational objective:
Most adverse drug reactions are predictable and due to known pharmacologic properties of the drug. Unpredictable reactions are less common and are typically driven by patient-specific genetics (eg, enzyme deficiency, immunologic idiosyncrasy).

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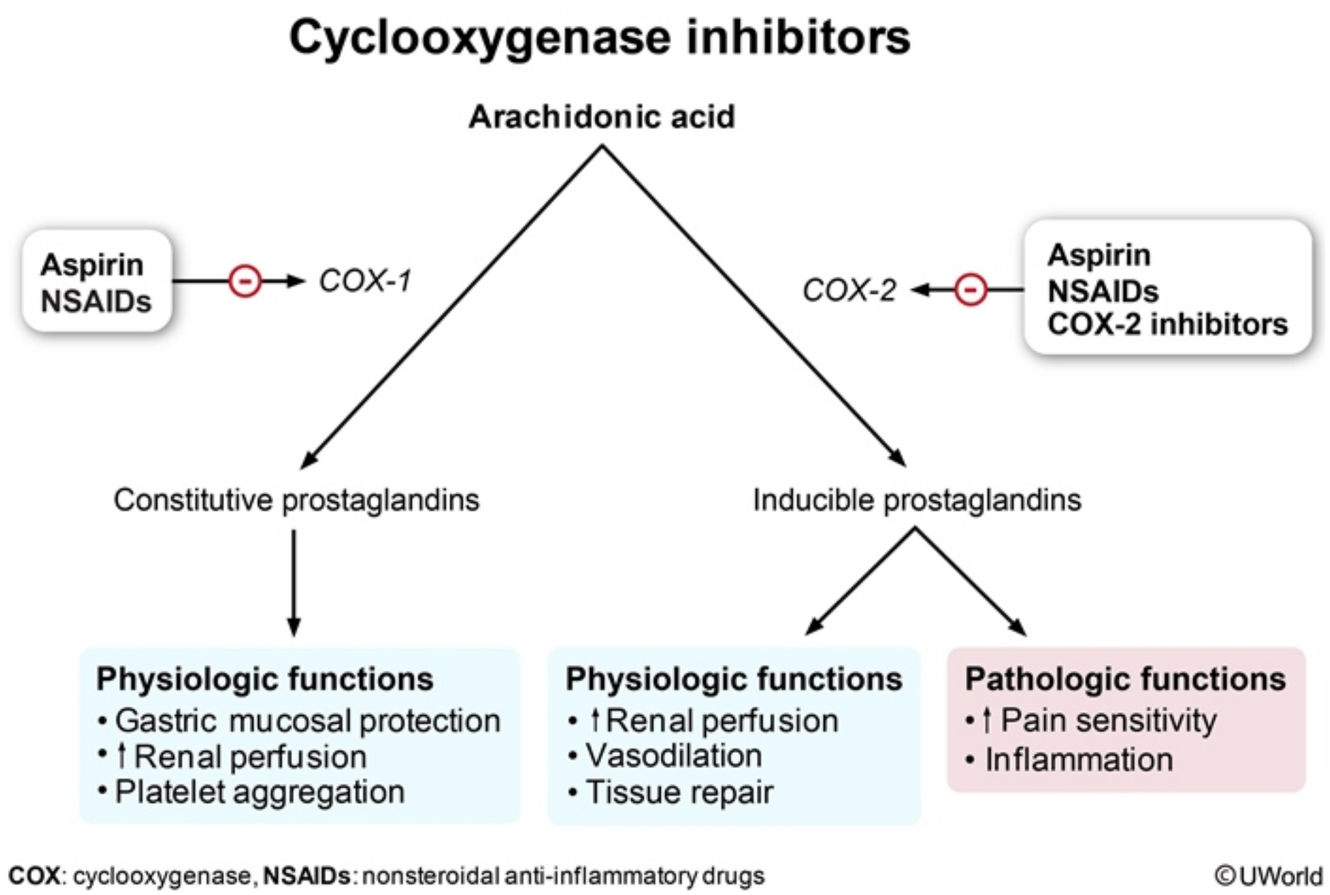

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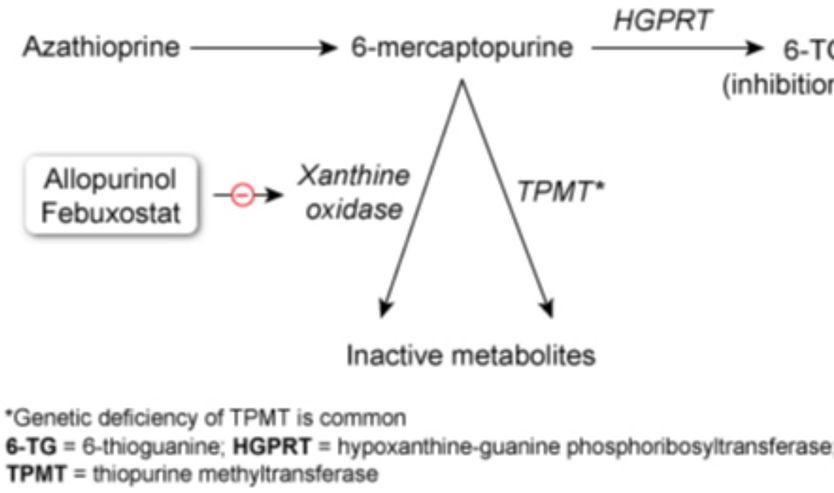

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Educational object
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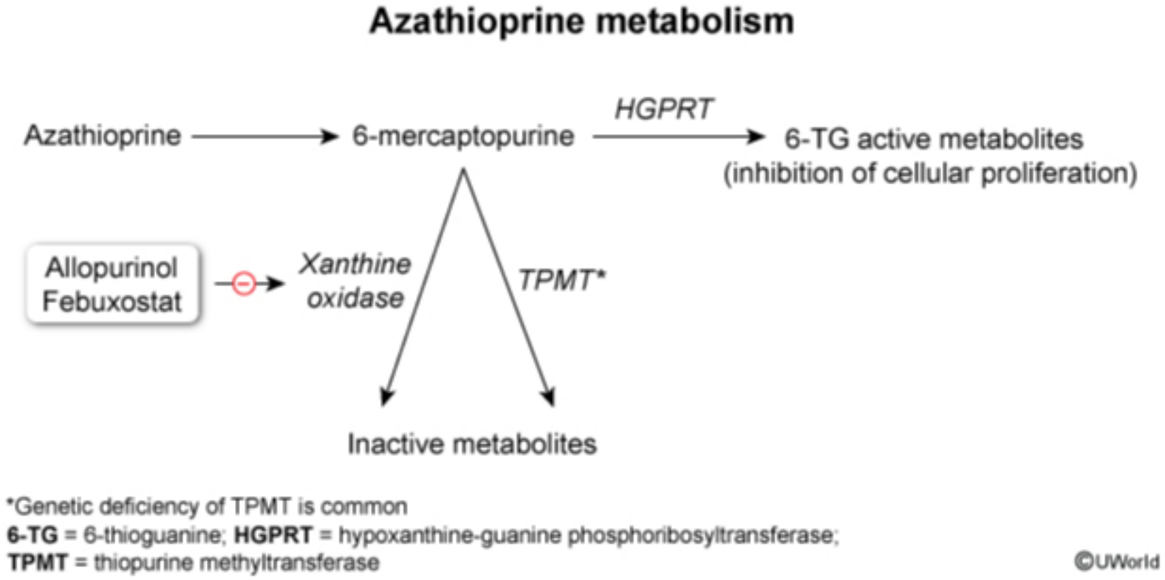

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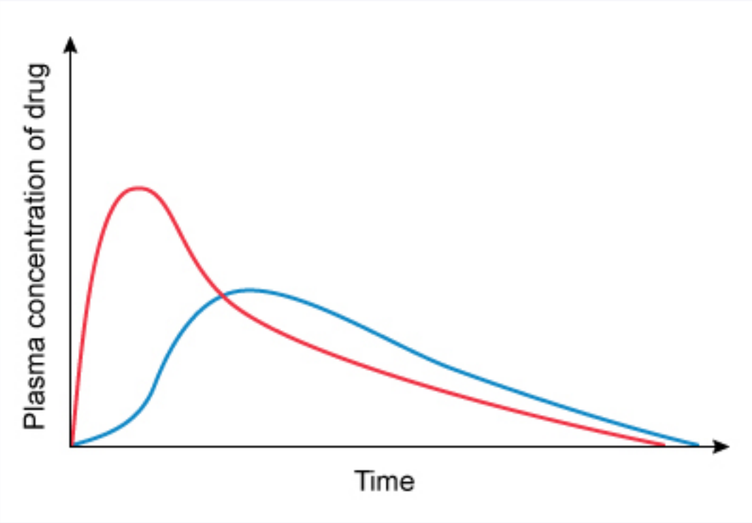
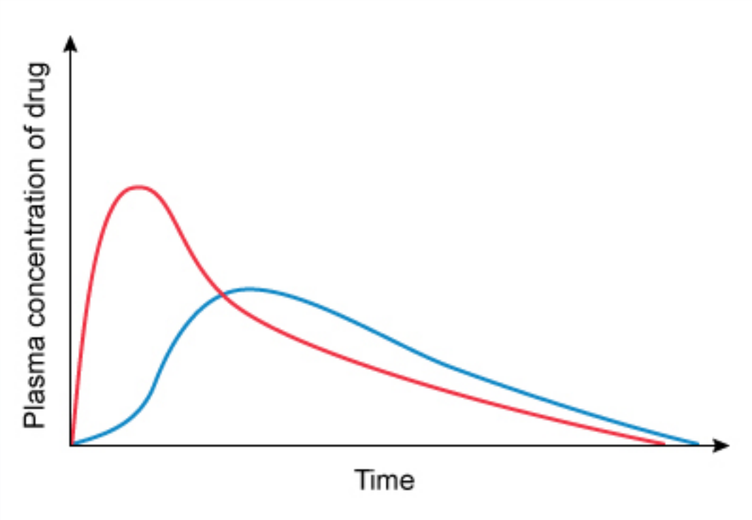
A pharmaceutical company in the final stages of designing a new nonsteroidal anti-inflammatory agent develops 2 different oral formulations of the drug. Two groups of volunteers are each administered a different formulation, and average plasma drug levels are monitored over the next 12 hours. The results are shown below:



Compared to the red curve, the formulation represented by the blue curve is most likely to have which of the following characteristics?

- A. Delayed intestinal absorption
- B. Enhanced CYP enzyme induction
- C. Increased biliary excretion
- D. Increased enterohepatic cycling
- E. Reduced first-pass metabolism

drug. Two groups of volunteers are each administered a different formulation, and average plasma drug levels are monitored over the next 12 hours. The results are shown below:



Compared to the red curve, the formulation represented by the blue curve is most likely to have which of the following characteristics?

- A. Delayed intestinal absorption (68%)
- B. Enhanced CYP enzyme induction (7%)
- C. Increased biliary excretion (2%)
- D. Increased enterohepatic cycling (8%)
- E. Reduced first-pass metabolism (13%)

Omitted
Correct answer

68%
Answered correctly

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The above graph shows the plasma drug concentration-time curves of the 2 different oral formulations. The one represented by the blue curve shows a **reduced and delayed peak** level relative to the red curve, which is consistent with a **sustained-release preparation**.

The absorption speed of an orally administered drug depends on the rate at which it dissolves in gastrointestinal fluids. Capsules and tablets can be designed with the active ingredient embedded in an insoluble matrix or encapsulated with coatings that dissolve at different rates to **delay intestinal absorption**. Slower drug absorption can have several advantages, including:

- Reduced incidence of adverse effects due to dampening of peak levels
- Longer duration of therapeutic effect due to prolonged absorption of the drug
- Improved patient compliance due to less frequent administration

These benefits make sustained-release preparations particularly useful for drugs with short half-lives (ie, allowing prolonged effect without need for multiple doses) or narrow therapeutic windows (ie, maintaining effective drug levels while minimizing absorption peaks).

(Choice B) Enhanced CYP enzyme induction by the blue formulation would cause increased drug metabolism over time as additional enzymes are synthesized, leading to decreased serum drug levels.

(Choice C) Increased biliary excretion of the blue formulation would be expected to decrease peak serum levels, but would not explain the delay in peak levels relative to the red curve.

(Choice D) Drugs that are excreted into the bile can undergo enterohepatic cycling, which can prolong the drug's effect longer than expected given the drug's half-life. However, increased enterohepatic cycling would not explain the initial delay in peak serum levels seen in the blue curve.

(Choice E) Reduced first-pass metabolism by the blue formulation would result in higher peak serum levels compared to the red curve due to increased quantities of drug entering the circulation.

Educational objective:
Sustained-release drug preparations have reduced and delayed peak levels compared to immediate-release preparations due to slower absorption in the gastrointestinal tract. Dampening of peak levels and prolonged absorption of the drug help maintain effective drug levels while minimizing toxicity.

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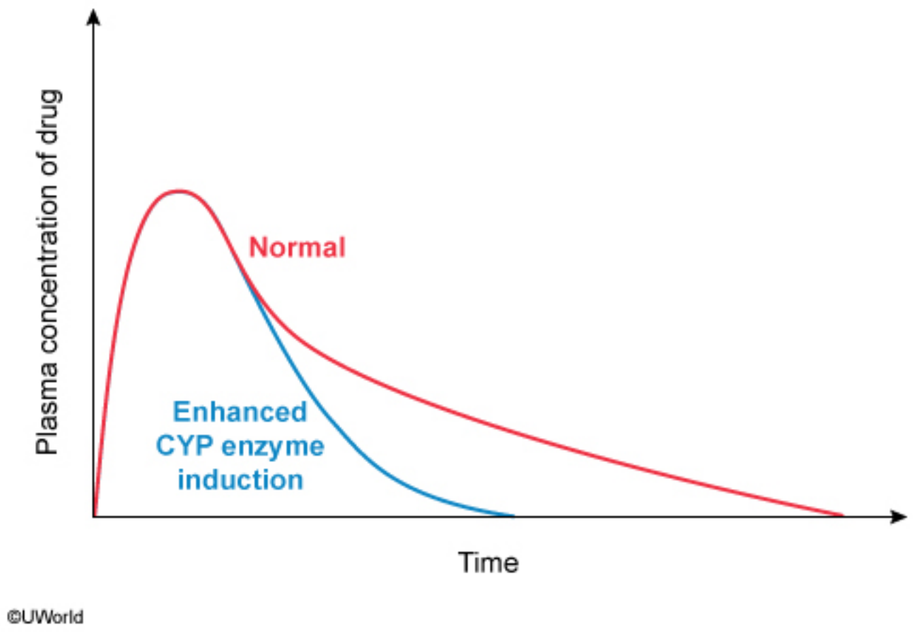

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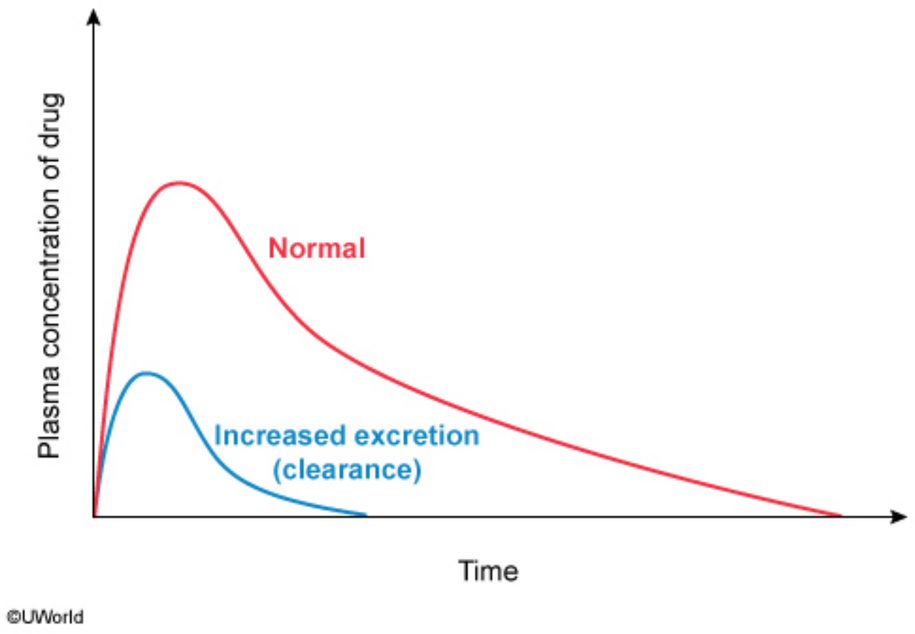

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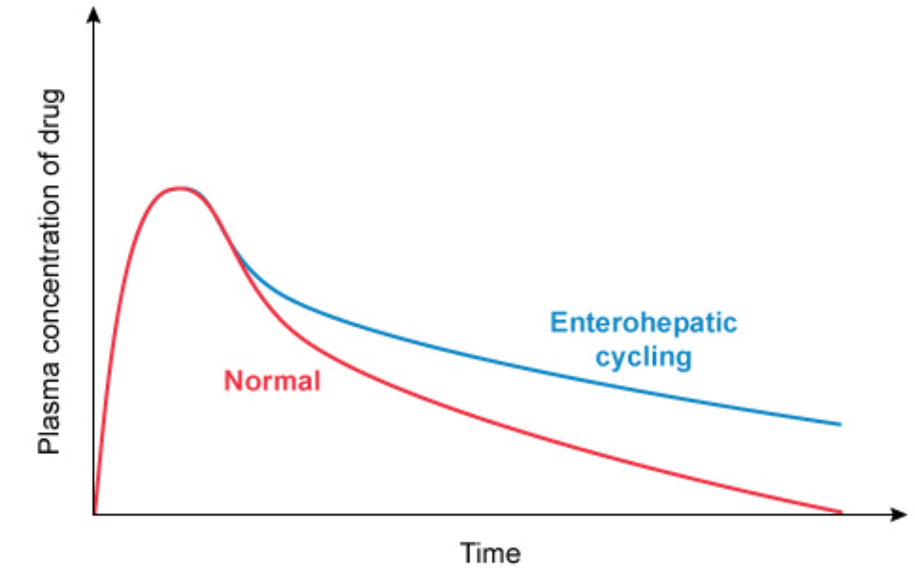

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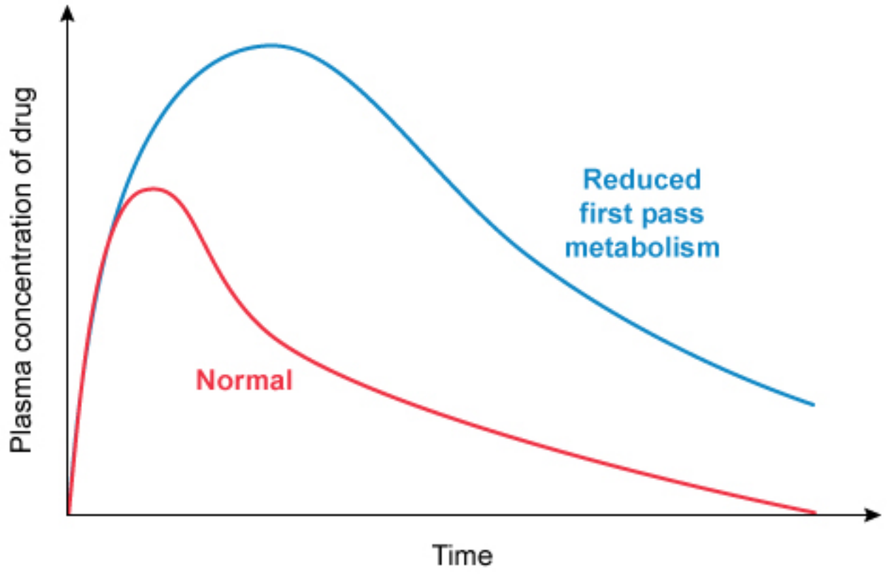

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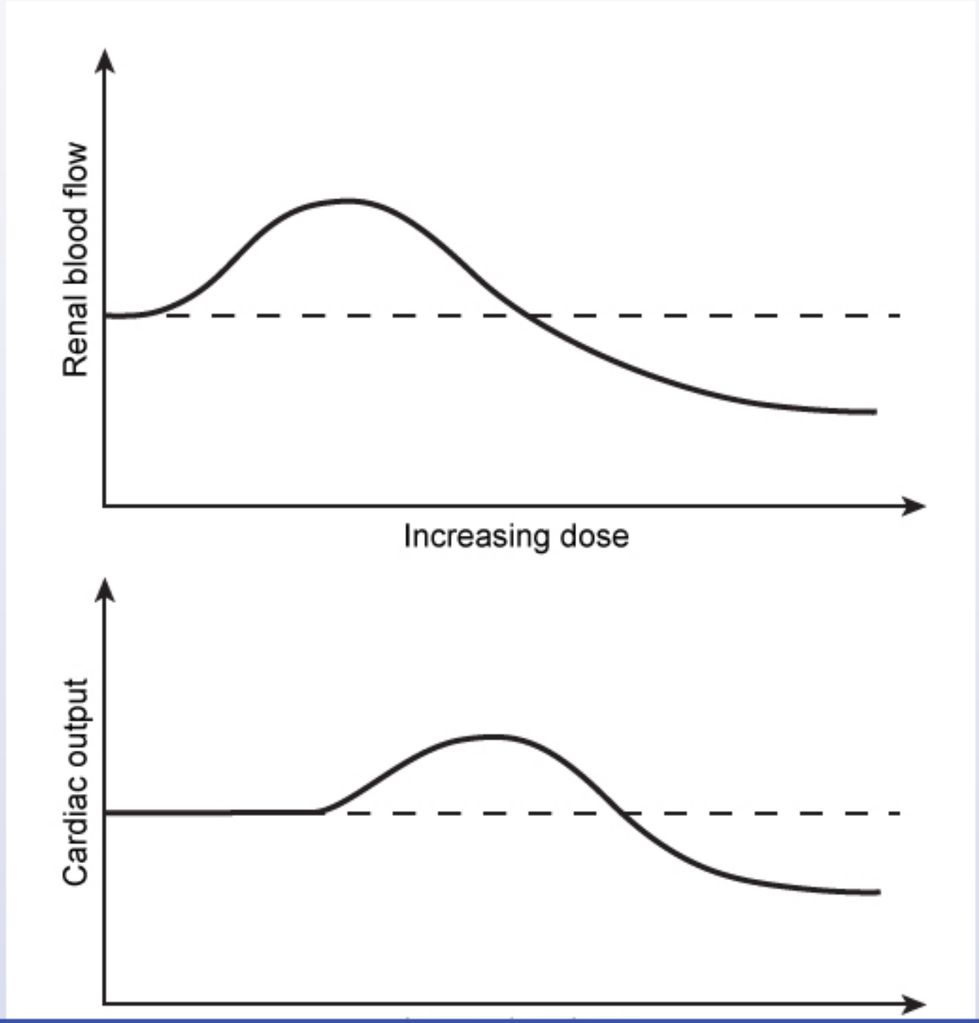
A medical student is conducting a pharmacology experiment to determine the effects of a certain drug. She infuses this drug intravenously over different dose ranges and measures several important hemodynamic parameters. Graphs plotting the observed changes in renal blood flow and cardiac output are shown below.



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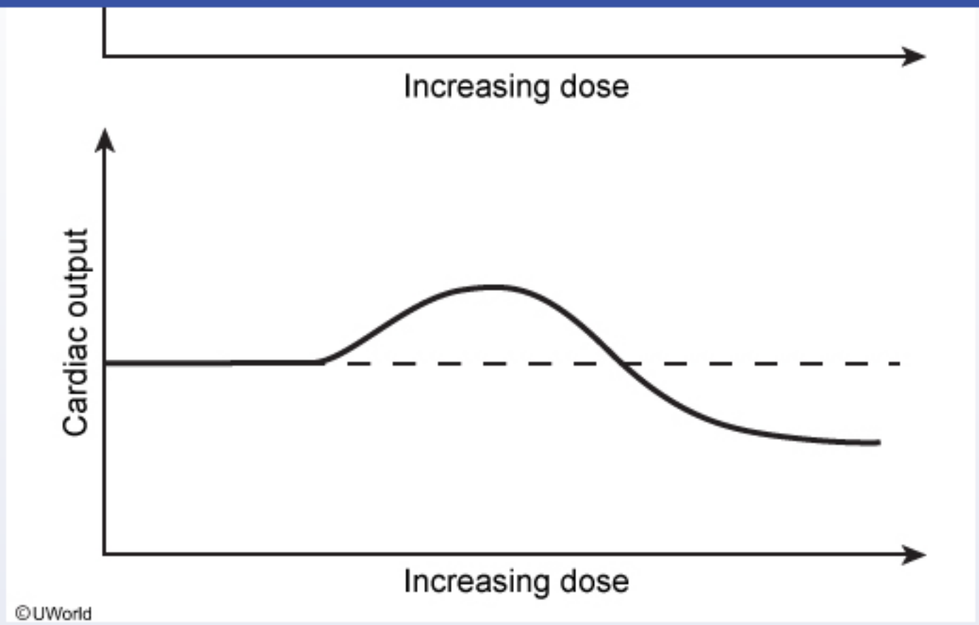

Which of the following drugs was most likely used in this experiment?

- A. Dopamine
- B. Edrophonium
- C. Epinephrine
- D. Esmolol
- E. Phenylephrine

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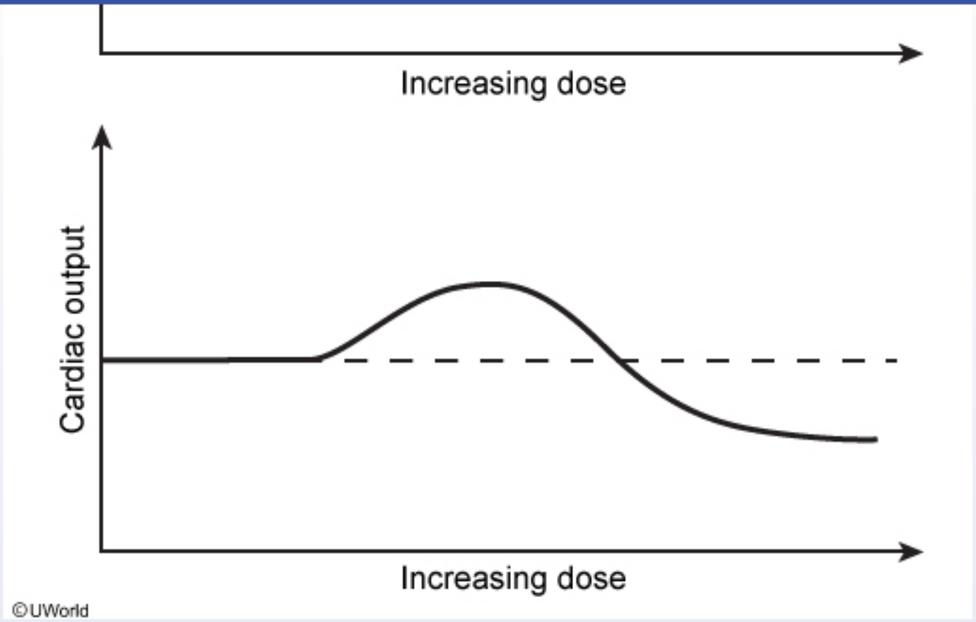

Which of the following drugs was most likely used in this experiment?

- ✓ A. Dopamine (67%)
- B. Edrophonium (1%)
- C. Epinephrine (19%)
- D. Esmolol (5%)
- E. Phenylephrine (5%)

Omitted
Correct answer

67%
Answered correctly

11 secs
Time Spent

06/02/2020
Last Updated

Hemodynamic effects of adrenergic agonists

- α_1: peripheral vasoconstriction, ↑ SVR
- β_1: ↑ heart rate & contractility, ↑ cardiac output
- β_2: peripheral vasodilation, ↓ SVR
- D_1: renal arteriolar vasodilation

Agonist	Receptor binding	SVR	Cardiac output	Renal blood flow
Dobutamine	$\beta_1 > \beta_2$	↓	↑	–
Dopamine	$D_1 > \beta_1 > \alpha_1$ (low-dose)	–/↓	↑	↑
	$\alpha_1 > \beta_1 > D_1$ (high-dose)	↑	–/↓	↓
Epinephrine	$\beta_1 > \beta_2 > \alpha_1$ (low-dose)	-/↓	↑	–
	$\alpha_1 > \beta_1 > \beta_2$ (high-dose)	↑	–/↓	↓
Isoproterenol	$\beta_1 = \beta_2$	↓	↑	–
Norepinephrine	$\alpha_1 = \beta_1 > \beta_2$	↑	–	↓
Phenylephrine	α_1	↑	↓	↓

SVR = systemic vascular resistance.

SVR = systemic vascular resistance.

Dopamine is an adrenergic agonist that has varying effects based on the dose. At **low doses**, dopamine stimulates **D1 receptors** in the renal vasculature and tubules, inducing an **increase in renal blood flow**, glomerular filtration rate, and sodium excretion. Vasodilation of the mesenteric, cerebral, and coronary vascular beds is also prominent at low doses.

As the dosage increases, dopamine begins to stimulate **$\beta_1$adrenergic receptors** in the heart, increasing cardiac contractility, heart rate, and systolic blood pressure. At the high end of the dose range, stimulation of **$\alpha_1$receptors** in the systemic vasculature leads to generalized vasoconstriction, which can result in decreased cardiac output due to the increased afterload.

(Choice B) Edrophonium is a short-acting acetylcholinesterase inhibitor used in the diagnosis of myasthenia gravis (ie, Tensilon test). Through its cholinergic effects, edrophonium reduces heart rate, cardiac conduction, and cardiac contractility.

(Choice C) Epinephrine increases heart rate, myocardial contractility, and cardiac output by stimulating β_1 receptors. At low doses, stimulation of β_2 receptors in the skeletal muscle vasculature produces vasodilation that can cause decreased blood pressure. At high doses, α_1-induced vasoconstriction in the skin and viscera becomes more pronounced. Epinephrine does not significantly increase renal blood flow (even at lower doses) due to the lack of D_1 receptor stimulation.

(Choice D) Esmolol is a cardioselective β_1 blocker with a short duration of action. Esmolol decreases heart rate, myocardial contractility, and cardiac conduction without affecting renal blood flow.

(Choice E) Phenylephrine is a selective α_1-adrenergic receptor agonist that causes a generalized increase in peripheral vascular resistance and blood pressure. Its use results in significant renal, splanchnic, and mesenteric vasoconstriction.

Educational objective:
Low-dose dopamine infusion stimulates D_1 receptors in the renal and mesenteric vasculature, resulting in vasodilation and increased blood flow to these sites. Increasing doses of dopamine stimulate β_1 and α_1 receptors, resulting in increased cardiac output and elevated systemic vascular resistance. At the high end of the dose range, the increase in afterload can result in decreased cardiac output.

Pharmacology	General Principles	Sympathomimetic agents
Subject	System	Topic

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A 64-year-old man is evaluated for persistent fever and weakness. He has a history of aortic valve replacement for aortic stenosis. Physical examination reveals a new cardiac murmur with scattered petechiae and splinter hemorrhages seen on his extremities. Echocardiogram shows a vegetation involving one of the aortic valve leaflets, and blood cultures grow enterococci. As part of the patient's treatment, 240 mg of intravenous gentamicin is started. The pharmacy calculates that, in this patient, gentamicin has a volume of distribution of 30 L, a half-life of 4 hours, and demonstrates first-order and one-compartment kinetics. Which of the following is the most likely serum drug concentration just before the next dose 8 hours later?

A. 0.5 mg/L

B. 1 mg/L

C. 1.5 mg/L

D. 2 mg/L

E. 3 mg/L

Submit

A 64-year-old man is evaluated for persistent fever and weakness. He has a history of aortic valve replacement for aortic stenosis. Physical examination reveals a new cardiac murmur with scattered petechiae and splinter hemorrhages seen on his extremities. Echocardiogram shows a vegetation involving one of the aortic valve leaflets, and blood cultures grow enterococci. As part of the patient's treatment, 240 mg of intravenous gentamicin is started. The pharmacy calculates that, in this patient, gentamicin has a volume of distribution of 30 L, a half-life of 4 hours, and demonstrates first-order and one-compartment kinetics. Which of the following is the most likely serum drug concentration just before the next dose 8 hours later?

- A. 0.5 mg/L (4%)
- B. 1 mg/L (4%)
- C. 1.5 mg/L (10%)
- ✓ D. 2 mg/L (75%)
- E. 3 mg/L (4%)

Omitted
Correct answer
D

75%
Answered correctly

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Time Spent

03/29/2020
Last Updated

Explanation

Optimal antibiotic therapy often requires monitoring of serum drug concentrations to ensure adequate dosing, which is necessary to achieve therapeutic levels while avoiding toxicity (eg, nephrotoxicity due to aminoglycosides). The highest level (peak) of drug concentration is usually ½ hour after intravenous or 1 hour after intramuscular dosing, whereas the lowest drug concentration (trough) occurs during the last ½ hour before the next dose.

Omitted
Correct answer
D

75%
Answered correctly

02 secs
Time Spent

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Explanation

Optimal antibiotic therapy often requires monitoring of serum drug concentrations to ensure adequate dosing, which is necessary to achieve therapeutic levels while avoiding toxicity (eg, nephrotoxicity due to aminoglycosides). The highest level (peak) of drug concentration is usually ½ hour after intravenous or 1 hour after intramuscular dosing, whereas the lowest drug concentration (trough) occurs during the last ½ hour before the next dose.

The **drug concentration** (mg/L) can be calculated by dividing the **drug dose** (mg) by the **volume of distribution** (V_D). V_D refers to the theoretically required volume (in liters) if the drug were contained completely in the plasma. It can vary depending on how well the drug distributes into tissues; the higher the V_D, the greater the drug binds to the tissues. When drug metabolism occurs via first-order kinetics, the **half-life** ($t_{1/2}$) represents the amount of time required to lower the drug concentration by **50%**.

In this example, the first dose of the drug is 240 mg, V_D is 30 L, and $t_{1/2}$ is 4 hours. The initial drug concentration is the dose (240 mg) divided by the V_D (30 L), which equals 8 mg/L. After the first half-life (4 hours), the drug concentration will decrease by half to 4 mg/L. After the next half-life (4 hours later, or 8 hours after the initial dose), the drug concentration will decrease by half again to 2 mg/L **(Choices A, B, C, and E)**.

Educational objective:
The half-life ($t_{1/2}$) of a drug is the time required to lower its concentration by 50%. The volume of distribution (V_D) refers to how well the drug distributes into tissues compared to plasma; the higher the V_D, the greater the drug distribution into the tissues. The drug concentration (mg/L) is equal to drug dose (mg) divided by V_D (L).

Pharmacology	General Principles	Serum drug levels and half-life
Subject	System	Topic

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An 8-year-old boy is brought to the office due to fatigue and intermittent bone pain for the past year. The patient's parents are concerned because he has stopped playing outside and mostly stays indoors watching television. On examination, height and weight are at the 5th percentile for age. The abdomen is soft and nontender with the liver palpable 4 cm below the right costal margin and the spleen palpable 8 cm below the left costal margin. Laboratory results show anemia and thrombocytopenia. A bone marrow biopsy shows macrophages with wrinkled, paperlike cytoplasm due to the accumulation of glycolipids within lysosomes. The patient is prescribed enzyme replacement therapy. Which of the following sets of pharmacologic properties best characterizes the administered medication?

	Route of administration	Entry into target cells	Structure
A.	Intravenous	Endocytosis	Protein
B.	Intravenous	Endocytosis	Steroid
C.	Intravenous	Passive diffusion	Protein
D.	Intravenous	Passive diffusion	Steroid
E.	Oral	Endocytosis	Protein
F.	Oral	Endocytosis	Steroid
G.	Oral	Passive diffusion	Protein
H.	Oral	Passive diffusion	Steroid

Submit

An 8-year-old boy is brought to the office due to fatigue and intermittent bone pain for the past year. The patient's parents are concerned because he has stopped playing outside and mostly stays indoors watching television. On examination, height and weight are at the 5th percentile for age. The abdomen is soft and nontender with the liver palpable 4 cm below the right costal margin and the spleen palpable 8 cm below the left costal margin. Laboratory results show anemia and thrombocytopenia. A bone marrow biopsy shows macrophages with wrinkled, paperlike cytoplasm due to the accumulation of glycolipids within lysosomes. The patient is prescribed enzyme replacement therapy. Which of the following sets of pharmacologic properties best characterizes the administered medication?

	Route of administration	Entry into target cells	Structure
✓ A. (58%)	Intravenous	Endocytosis	Protein
B. (5%)	Intravenous	Endocytosis	Steroid
C. (6%)	Intravenous	Passive diffusion	Protein
D. (7%)	Intravenous	Passive diffusion	Steroid
E. (14%)	Oral	Endocytosis	Protein
F. (2%)	Oral	Endocytosis	Steroid
G. (2%)	Oral	Passive diffusion	Protein
H.	Oral	Passive diffusion	Steroid

This patient has **Gaucher disease**, an autosomal recessive condition caused by a **deficiency of lysosomal beta-glucocerebrosidase**. This deficiency leads to the accumulation of glucocerebroside, a glycolipid component of cell membranes, within the lysosomes of macrophages, giving them the classic appearance of wrinkled tissue paper. Characteristic symptoms (eg, hepatosplenomegaly, pancytopenia, bone pain) develop as lipid-laden macrophages accumulate in the body's tissues (eg, spleen, liver, and bone).

Lysosomal storage diseases can be treated through the delivery of a **replacement enzyme** into the lysosomes of affected cells; in the case of Gaucher disease, **recombinant glucocerebrosidases** (eg, imiglucerase) are available to replace the deficient enzyme. Almost all human enzymes, including lysosomal enzymes, are large polypeptides (eg, proteins) **(Choice B)**. Although the oral route is often preferred for drug administration, most peptide-based drugs (eg, insulin, immunoglobulins) cannot be efficiently absorbed by the gastrointestinal tract due to the intestinal epithelial barrier and extensive proteolysis that takes place in the stomach and duodenum. As a result, **large polypeptides** such as a glucocerebrosidase must be **administered intravenously** to achieve adequate circulating levels.

Once in the circulation, exogenous glucocerebrosidase can enter cells by binding to **mannose 6-phosphate receptors**. These receptors are found in the Golgi network, where they help route newly synthesized lysosomal proteins (tagged by mannose 6-phosphate residues). They are also expressed **on the cell surface**, where they bind free lysosomal enzymes that are accidentally secreted. Exogenous glucocerebrosidase can bind to these cell surface receptors, inducing **endocytosis** of the bound enzyme. It is then carried by endosomes to lysosomes, where it can degrade accumulated glucocerebrosides, reducing disease manifestations.

(Choices C and D) Enzymes are large, polar polypeptides that are unable to effectively cross the cell membrane by passive diffusion. In contrast, steroid-based drugs are typically hydrophobic and can easily cross cell membranes by passive diffusion. However, steroidal drugs function by binding to receptors; they do not directly catalyze reactions.

(Choices E, F, G, and H) Unlike in lysosomal storage diseases, enzyme replacement therapy for pancreatic exocrine insufficiency is administered orally because pancreatic digestive enzymes normally function within the gastrointestinal lumen.

Educational objective:
Certain lysosomal storage diseases, including Gaucher disease, can be treated with enzyme-replacement therapy (eg, recombinant glucocerebrosidase). Because enzymes are large proteins that cannot be orally absorbed, the replacement enzyme must be administered intravenously. Entry into the cell occurs by endocytosis after the replacement enzyme binds to mannose 6-phosphate receptors on the cell surface.

Lysosomal storage diseases can be treated through the delivery of a **replacement enzyme** into the lysosomes of affected cells; in the case of Gaucher disease, **recombinant glucocerebrosidases** (eg, imiglucerase) are available to replace the deficient enzyme. Almost all human enzymes, including lysosomal enzymes, are large polypeptides (eg, proteins) **(Choice B)**. Although the oral route is often preferred for drug administration, most peptide-based drugs (eg, insulin, immunoglobulins) cannot be efficiently absorbed by the gastrointestinal tract due to the intestinal epithelial barrier and extensive proteolysis that takes place in the stomach and duodenum. As a result, **large polypeptides** such as a glucocerebrosidase must be **administered intravenously** to achieve adequate circulating levels.

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Educational objective:
Certain lysosomal storage diseases, including Gaucher disease, can be treated with enzyme-replacement therapy (eg, recombinant glucocerebrosidase). Because enzymes are large proteins that cannot be orally absorbed, the replacement enzyme must be administered intravenously. Entry into the cell occurs by endocytosis after the replacement enzyme binds to mannose 6-phosphate receptors on the cell surface.

Pharmacology	General Principles	Drug structure and properties
Subject	System	Topic

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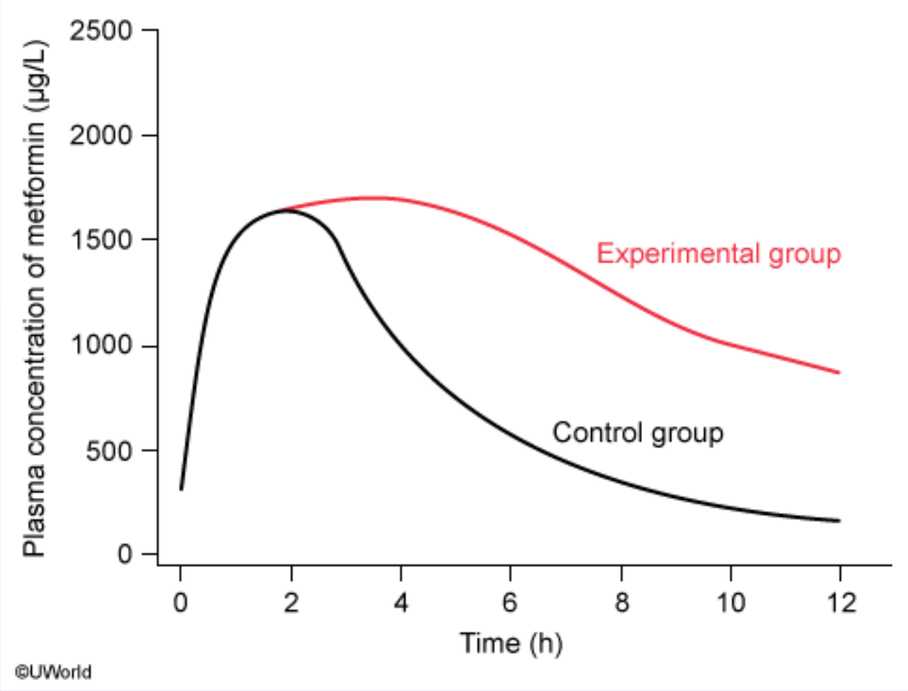
Researchers investigating the effects of heart failure on the pharmacokinetics of antidiabetic medications develop a cohort of experimental animals with anthracycline-induced heart failure. The experimental animals are then administered an oral dose of metformin, and serum levels are monitored over time. The test is repeated in control animals with normal heart function and the results are shown below:



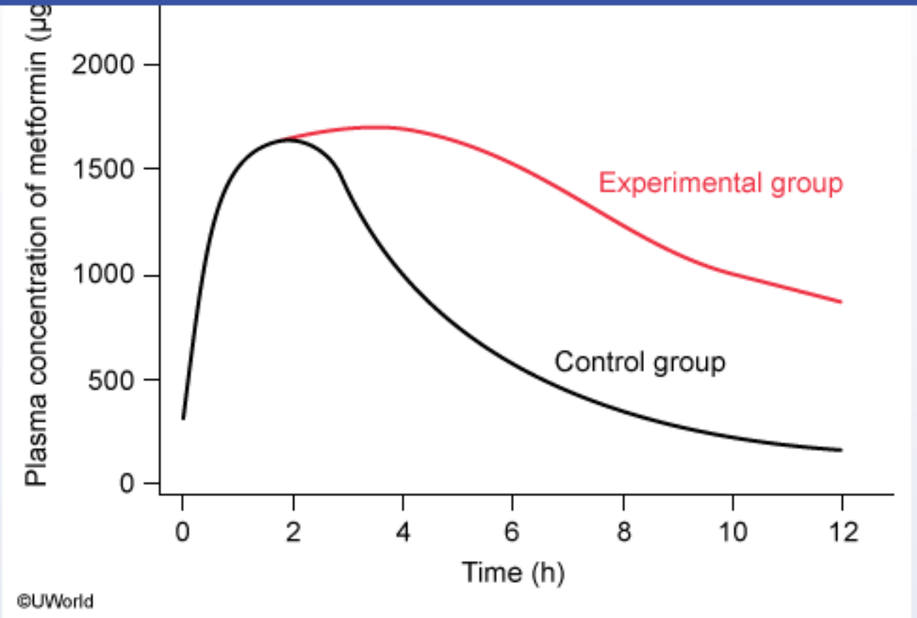
Which of the following best explains the change in serum metformin levels seen in the experimental animals?

A. Cytochrome P450 inhibition

B. Decreased renal blood flow

C. Extracellular fluid accumulation

D. Hepatic venous congestion



Which of the following best explains the change in serum metformin levels seen in the experimental animals?

- A. Cytochrome P450 inhibition
- B. Decreased renal blood flow
- C. Extracellular fluid accumulation
- D. Hepatic venous congestion
- E. Intestinal wall edema

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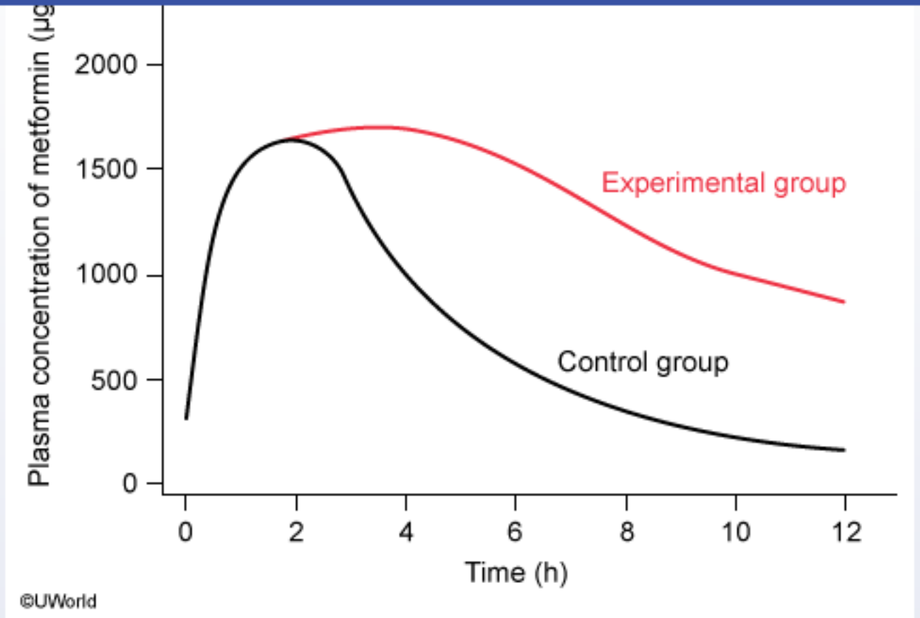

Which of the following best explains the change in serum metformin levels seen in the experimental animals?

- A. Cytochrome P450 inhibition (6%)
- ✓ B. Decreased renal blood flow (78%)
- C. Extracellular fluid accumulation (5%)
- D. Hepatic venous congestion (8%)
- E. Intestinal wall edema (0%)

Omitted
Correct answer

78%
Answered correctly

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04/23/2020
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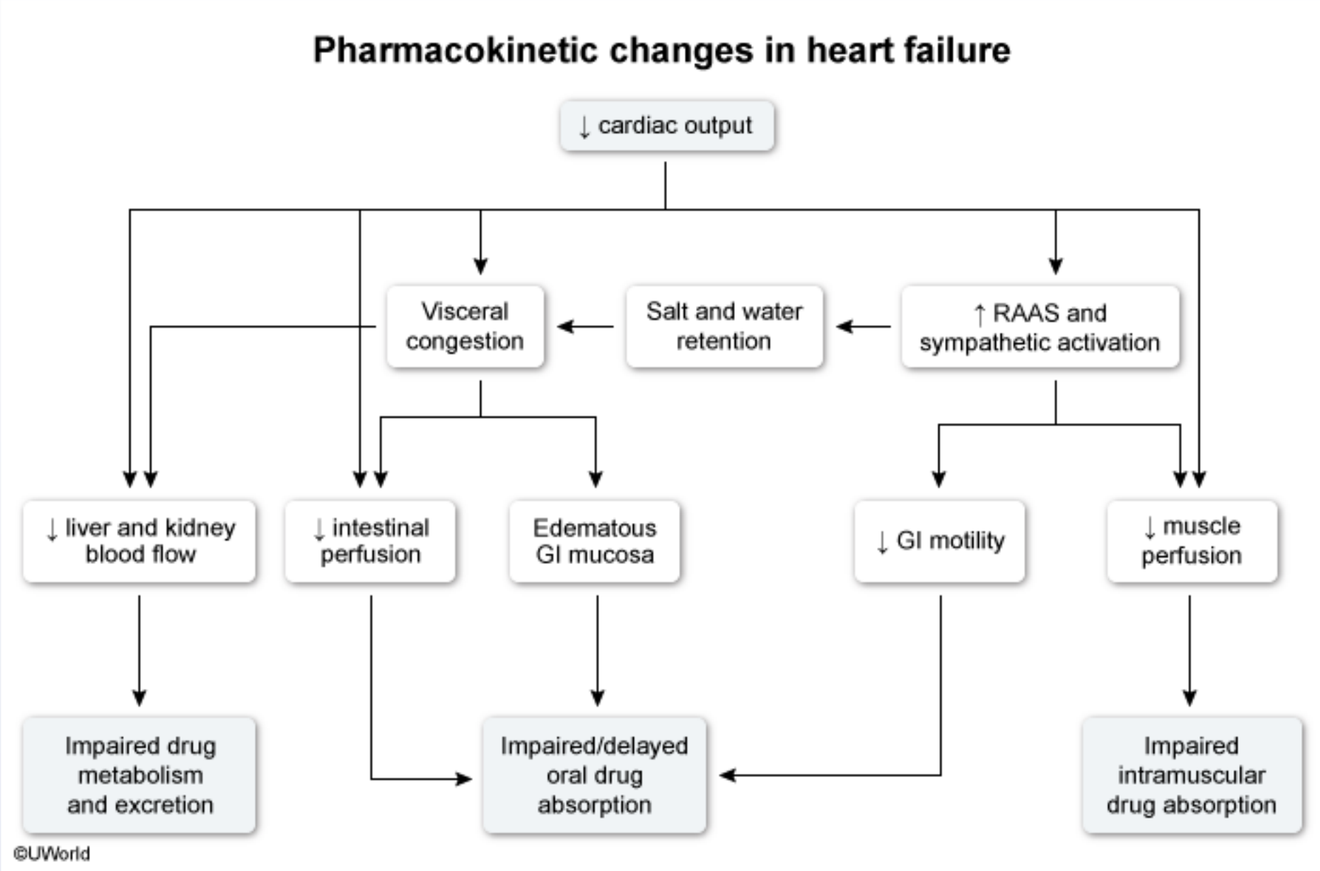

Heart failure can cause changes in pharmacokinetic parameters that can alter drug effectiveness and lead to increased toxicity. **Decreased cardiac output** leads to tissue hypoperfusion, lowering the volume of distribution of many drugs and **reducing perfusion** of organs responsible for **drug clearance** (eg, liver, kidneys). This can result in higher serum drug levels and a prolonged elimination phase, which can be particularly important for drugs with a narrow therapeutic index (eg, digoxin, antiarrhythmics).

In this example, **serum metformin levels** are seen to **increase** in animals with experimentally induced heart failure. Because metformin is **renally cleared**, this effect is most likely due to **decreased renal blood flow** as a result of reduced cardiac output. Because of the risk of lactic

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In this example, **serum metformin levels** are seen to **increase** in animals with experimentally induced heart failure. Because metformin is **renally cleared**, this effect is most likely due to **decreased renal blood flow** as a result of reduced cardiac output. Because of the risk of lactic acidosis, metformin should be used with caution in patients with heart failure or impaired renal function from other causes.

(Choices A and D) Heart failure frequently causes high central venous pressure and hepatic congestion. The resulting impairment in nutrient and oxygen delivery leads to hepatocellular damage and downregulation of CYP enzymes involved in drug metabolism. Reduced hepatic blood flow also results in decreased drug delivery to the liver, further impairing hepatic drug metabolism and clearance. However, metformin is not metabolized by the liver; it is excreted unchanged by the kidney.

(Choice C) Decreased tissue perfusion in heart failure typically leads to a reduced volume of distribution of most drugs. Although the *extracellular fluid accumulation* that occurs in decompensated heart failure can potentially increase the volume of distribution of water-soluble drugs, this increased distribution volume would result in a *decrease* in serum drug levels.

(Choice E) Increased central venous pressure in heart failure can lead to intestinal wall edema with increased intestinal wall thickness. This can result in delayed or decreased intestinal drug absorption. However, this effect would be expected to cause reduced serum drug concentrations and delayed peak levels.

Educational objective:
Heart failure leads to reduced liver and kidney perfusion, resulting in reduced drug clearance. Metformin is excreted unchanged by the kidney; therefore, patients with significant renal insufficiency due to heart failure or other causes (eg, chronic kidney disease) are at increased risk of toxicity (eg, lactic acidosis).

Pharmacology	General Principles	Drug metabolism and clearance
Subject	System	Topic

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A healthy 22-year-old man who weighs 70 kg (154.3 lb) volunteers for a phase I clinical trial investigating the properties of a newly developed antimicrobial agent. The drug is found to have a volume of distribution of 10 L and exhibits first-order elimination kinetics. The rate of drug clearance is calculated to be 7 L/hr. It is determined that repeating the second dose when 75% of the drug is eliminated will minimize toxicity while maintaining trough levels above the minimum inhibitory concentration. Based on these research findings, which of the following is the most appropriate dosing interval for this drug?

A. 1 hour

B. 1.5 hours

C. 2 hours

D. 2.5 hours

E. 3 hours

Submit

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- A. 1 hour (21%)
- B. 1.5 hours (26%)
- ✓ C. 2 hours (36%)
- D. 2.5 hours (8%)
- E. 3 hours (6%)

Omitted
Correct answer
C

36%
Answered correctly

03 secs
Time Spent

03/03/2020
Last Updated

Explanation

The **half-life ($t_{1/2}$)** is the time required for the plasma concentration of a drug with first-order elimination kinetics to decrease by 50%. It depends on the drug's physicochemical properties such as lipid solubility, protein binding, and metabolic conversion or elimination pathways. The half-life of a drug after administration of a single dose can be calculated from its **volume of distribution (V_d)** and **clearance rate (CL)**:

$$t_{1/2} = (0.7 \times V_d) / CL$$

The half-life can be used to estimate how much of the drug has been eliminated from the body after a specific amount of time. At time zero, 100%

Explanation

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The half-life can be used to estimate how much of the drug has been eliminated from the body after a specific amount of time. At time zero, 100% of the drug is present following intravenous dosing. With the passage of each subsequent half-life, half of the remaining drug is eliminated. After 5 half-life intervals, a drug is almost completely eliminated from the body.

First-order drug kinetics	
Elapsed half-lives	**Amount eliminated**
0	0%
1	50%
2	75%
3	87.5%
4	93.75
5	96.875%

With respect to the clinical trial in this scenario, the equation above can be used with the provided values to calculate the half-life as follows:

$$t_{1/2} = (0.7 \times 10\ L) / 7L/hr = 1\ hour$$

It will take 2 half-life intervals to eliminate 75% of the drug. Therefore, it will take 2 hours to excrete 75% of the drug.

$t_{1/2} = (0.7 \times V_d) / CL$

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Educational objective:
The half-life ($t_{1/2}$) is a measure of how quickly a drug with first-order kinetics is eliminated from the body. A drug is almost completely eliminated after 5 half-life intervals. The half-life can be calculated from the drug's volume of distribution (V_d) and clearance rate (CL) using the equation: **$t_{1/2} = (0.7 \times V_d) / CL$**.

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Pharmacology	General Principles	Serum drug levels and half-life
Subject	System	Topic

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